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**A mathematical model based method for  
converting venous values of acid-base and  
oxygenation status to arterial values  
– description and evaluation**

**Ph.D. thesis**

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## Summary

Arterial blood analysis with description of acid-base, oxygenation and electrolyte status is an important tool for assessing the metabolic, cardiovascular and respiratory status of a patient. In intensive care units and other high-dependency units sampling of arterial blood is performed many times a day. In emergency departments and other non-intensive care departments such as pulmonary and nephrology departments arterial blood gas analysis is also an important part of daily monitoring and is done by arterial puncture.

In medical and surgical wards arterial blood sampling are not routine and are only taken when a patient has deteriorated or the clinician needs further information.

In contrast, a peripheral venous blood sample is often one of the first diagnostic tests performed on admission to the hospital, and on in-patients whose status deteriorates.

Venous blood and especially peripheral venous blood is generally not used to describe the metabolic and respiratory status of a patient, except in some situations where central venous blood can be of value.

A number of studies have investigated the role of venous blood measurements for evaluating acid-base status, most of these studies reporting the correlation between arterial and venous blood using only one variable (pH or  $PCO_2$ ). In general these studies have found a good correlation in non-cardiac arrest patients with regard to pH and a weaker correlation regarding  $PCO_2$ . No correlation exists between arterial and venous  $PO_2$ .

Methods have been developed to “arterialise” venous blood by warming the sampling site, causing blood flow to increase to such an extent that the venous blood would have the same characteristics as the arterial blood. These methods require extra equipment and time and are therefore not so clinically useful.

In this thesis a method for converting venous blood values, supplemented with a pulse oximetry reading, to arterial values with both acid-base and oxygenation values included is described and evaluated.

The thesis includes data from two studies, one including 103 adult patients. The second study includes 15 children.

In chapter one the new method is described in detail including the physiological assumptions, sensitivity analysis and possible limitations of the method.

The principle of the method is to calculate arterial values by simulating, with the help of mathematical models, the reverse transport of blood from the veins to the arteries until the simulated arterial oxygenation matches that measured by pulse oximetry.

The use of the method is illustrated with data from three patients with different acid-base, haemodynamic, and metabolic conditions. The sensitivity of the method is tested for measurement errors, errors due to physiological assumptions and errors due to air bubbles in the blood.

The sensitivity tests show that the method is very insensitive to these points except in the calculation of  $PO_2$  from  $SpO_2$  above 97 % due to the flat slope of the oxygen dissociation curve (ODC).

In chapter two the data from the adult study are described. The measured values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from arterial and venous blood, the venous blood being sampled from peripheral, central and mixed veins are compared.

The results indicate that the venous values of pH, corrected for bias, can give arterial values within or close to laboratory acceptable performance criteria. For PCO<sub>2</sub> this is also true, except for peripheral blood.

For PO<sub>2</sub> values of arteriovenous bias is not randomly distributed and the size of bias and SD clearly indicates that venous blood values can not be used to estimate arterial values of PO<sub>2</sub>.

In chapter three data from the adult study are used with application of the venous to arterial conversion method to calculate arterial values from measured venous values.

The results show that the calculated values of arterial pH and PCO<sub>2</sub> were very close to the measured arterial values regardless of the venous sampling site, but that calculations made from peripheral venous blood were significantly more precise than those from central venous blood. The standard deviation (SD) of calculated values of pH and PCO<sub>2</sub> was similar to the SD of consecutive arterial samples.

For peripheral venous blood the SD of calculated arterial pH and PCO<sub>2</sub> are half that seen for direct correlation between measured arterial and venous blood, and as such the new method offers a great improvement on the information obtained from peripheral venous blood.

For SpO<sub>2</sub> < 97 %, the method calculates PO<sub>2</sub> with a similar variability as between consecutive arterial blood samples. For SpO<sub>2</sub> ≥ 97 % the method is not able to predict PO<sub>2</sub> within an acceptable clinical range. In clinical use however the most important patients are those with low values of SpO<sub>2</sub>, thus making the method potentially very useful for screening and monitoring of these patients.

In chapter four the results from the child study are reported.

First the measured values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from venous and capillary blood were compared to measured arterial values. Then the venous to arterial conversion method was applied to the measured venous and capillary values.

The results of application of the method on pH and PCO<sub>2</sub> were similar to the results from the adult study with a reduction of arterio-venous bias and a marginally larger SD than in the adult study.

The method applied on PO<sub>2</sub> shows a larger SD than in the adult study, partly explained by a lesser precision of SpO<sub>2</sub> measurement in the pediatric population.

The results indicate a possible use of the method in the pediatric population, as the application of the method on sampled blood either from venous or capillary sites is safe and could spare the child from an arterial puncture.

## Introduction

Arterial blood gas analysis with description of the acid-base, oxygenation and electrolyte status is an important tool, often used to assess the metabolic, cardiovascular and respiratory status of the patient. In intensive care units and other high-dependency units sampling of arterial blood is often performed many times a day, as most of the patients have an indwelling arterial catheter for monitoring arterial blood pressure. In emergency departments and other non-intensive care departments where arterial blood gas analysis still is an important part of daily monitoring, i.e. pulmonary, nephrology, endocrinology (diabetes) and neonatal departments, patients do not routinely have arterial catheters. In other medical and surgical wards arterial blood sampling are not routine and are usually only taken when a patient has deteriorated or the clinician needs further information. In these departments the arterial blood sample is obtained by needle puncture of an artery, often demanding specially trained staff (Fagan & Cece 1999). An arterial puncture bears risks of bleeding, haematoma, emboli/thrombosis or nerve damage and is associated with substantial pain (Gillies et al. 1979; Spies & Berlin 1998).

In contrast, large numbers of peripheral venous blood samples are taken easily and safely in almost every hospital department. In fact a peripheral venous blood sample is often one of the first diagnostic tests performed on admission to the hospital, and on in-patients whose status deteriorates. The information obtained from the peripheral venous blood does not normally include values relevant to the acid-base status except typically the standard bicarbonate (SBC) and the haemoglobin (Hb). It is generally accepted that venous blood and especially peripheral venous blood does not describe the metabolic and respiratory status of a patient, except in some situations with cardiovascular collapse, where central venous blood can be of value in assessing the acid-base status. (Radiometer Medical A/S 1997).

Peripheral venous blood samples are usually taken aerobically with no attempt to ensure a constant level of oxygen and carbon dioxide in the sample and therefore these values would probably not reflect the true values in the blood.

A number of studies have investigated the role of venous blood measurements for evaluating acid-base status, with either peripheral venous, central venous, mixed venous or capillary blood (Adroque et al. 1989; Brandenburg & Dire 1998; Brandi et al. 1995; Gambino 1959; Gennis et al. 1985; Gokel et al. 2000; Harrison et al. 1997; Kelly et al. 2001; Rang et al. 2002; Sutton et al. 1967; Weil et al. 1986; Yildizdas). Most of these studies have investigated the correlation between arterial and venous values in only a single variable (pH or  $PCO_2$ ) at a single sampling site. In non-cardiac arrest patients, these studies have found a good correlation between arterial and venous blood in values of pH taken from different sampling sites, with a difference of arterial and venous pH of about 0.04 and a SD of about 0.04. Fewer studies have been performed comparing arterial and venous values of  $PCO_2$  (Adroque et al. 1989; Brandi et al. 1995; Gennis et al. 1985; Harrison et al. 1997; Rang et al. 2002; Sutton et al. 1967; Weil et al. 1986). Only three studies have compared arterial and peripheral venous blood, these finding an

arteriovenous difference in  $\text{PCO}_2$  of -0.05 to -1.0 kPa with a SD of 0.5 to 1.0 kPa (Gennis et al. 1985; Rang et al. 2002; Toftegaard et al. 2008). For central venous blood, studies comparing arterial and venous values of  $\text{PCO}_2$  are few (Adroque et al. 1989; Brandi et al. 1995; Weil et al. 1986; Toftegaard et al. 2008) and have not consistently found a good correlation. Four studies have investigated the correlation between arterial and venous  $\text{PO}_2$  or  $\text{SaO}_2$ , finding in general a poor correlation (Harrison et al. 1997; Sutton et al. 1967; Yildizdas et al. 2004; Toftegaard et al. 2008). In addition, for many of these studies, arterial and venous blood samples were not taken simultaneously with intervals of up to ten minutes between sampling the venous and arterial blood (Brandenburg & Dire 1998) and with no documentation for circulatory stability between the blood samples (Gennis et al. 1985; Gokel et al. 2000; Rang et al. 2002). Despite the somewhat positive results of the previous studies indicating a possible role for venous blood pH and perhaps  $\text{PCO}_2$  for evaluating acid-base status, venous blood measurements have not gained clinical acceptance.

In recognition of the problems with arterial blood sampling methods have been developed to “arterialise” venous blood by warming the sampling site, causing blood flow to increase to such an extent that the venous blood would have the same characteristics as the arterial blood. (Collis & Neaverson 1967; Forster et al. 1972; van der Weerd et al. 2002; Zello et al. 1990). The methods require extra equipment and the procedure takes about 15 min before the hand reaches the appropriate temperature. In clinical practice this method is probably not useful.

The purpose of this thesis was to develop and evaluate a method for converting anaerobically taken venous blood values supplemented with arterial oxygen saturation measured by a pulse oximeter to arterial values with both acid-base and oxygenation values included. The clinical value of using peripheral venous blood is explored in detail, as a positive result would make acid-base and oxygenation status available to a greater number of patients in clinical situations.

Two clinical studies are reported.

The first study includes 103 adult evaluable patients. The correlation between measured peripheral, central or mixed venous blood values of pH,  $\text{PCO}_2$  and  $\text{PO}_2$  compared to simultaneously taken arterial blood values of pH,  $\text{PCO}_2$  and  $\text{PO}_2$  are described. The same blood gas and oxygenation values resulting from application of the venous to arterial conversion method on these data are then described in detail.

The second study not published, includes 15 children. In this study the correlation between measured venous or capillary blood values of pH,  $\text{PCO}_2$  and  $\text{PO}_2$  compared with simultaneously taken arterial blood values are described. The blood gas and oxygenation values resulting from application of the venous to arterial conversion method on these data are also described in detail.



The thesis is divided in four chapters followed by a conclusion.

**Chapter one** gives a description of the venous to arterial conversion method in detail including the physiological assumptions, sensitivity analysis and the possible limitations of the method.

**Chapter two** describes data obtained in the adult patient clinical study, with values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from peripheral, central and mixed venous blood samples directly compared to simultaneously taken arterial blood samples.

**Chapter three** describes the results of application of the venous to arterial conversion method on the measured venous blood values obtained in the adult patient clinical study, from the three different sampling sites, and subsequently a comparison between the calculated arterial values and the simultaneously measured arterial values.

**Chapter four** describes the unpublished results of a pilot study on 15 children where venous and arterialised capillary blood values are compared to simultaneously taken arterial blood values, and furthermore the results of application of the venous to arterial conversion method on the venous and capillary blood values.

## Chapter 1

In this chapter the venous to arterial conversion method will be described in detail. The chapter is based on article number I.

The principles in the method are applicable to venous blood sampled from all sites, peripheral, central and mixed, but as will be explored in detail later peripheral blood gave the most accurate results.

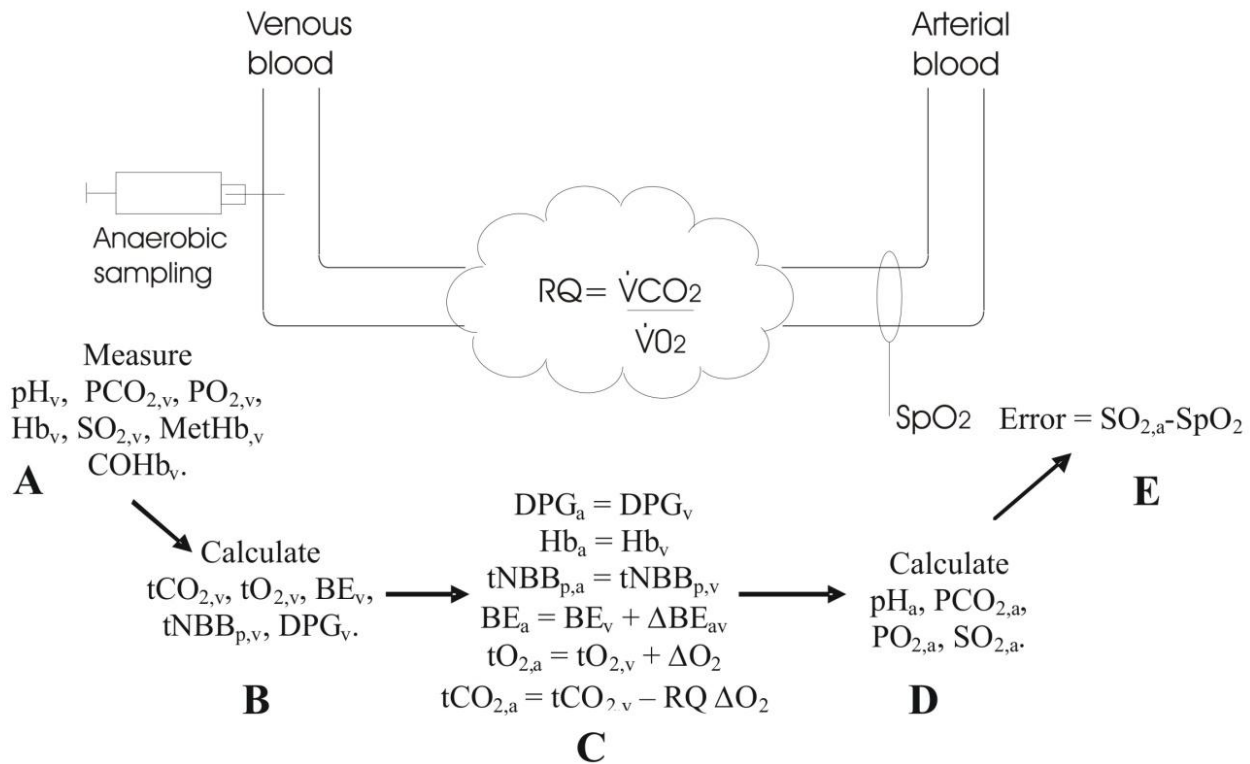


Figure 1 : The venous to arterial conversion method (taken from Rees et al. 2006 with permission from Elsevier)

Figure 1 illustrates the method for calculating values of the acid-base and oxygenation status of arterial blood from values in venous blood, supplemented by arterial oxygen saturation measured with a pulse oximeter. The principle of the method is that venous values of blood gas and oxygenation can be mathematically transformed into arterial values by simulating the transport of blood back through the tissues. To perform this simulation two assumptions are required. First, it is assumed that the amount of strong acid added to the blood on its passage through the tissues is very small or zero, such that the change in base excess (BE) from the venous sampling site to the arterial site ( $\Delta BE_{av}$ ) is approximately zero.

Base Excess is defined here as the concentration of strong acid necessary to titrate fully oxygenated blood to a  $pH_p = 7.4$ , at a  $PCO_2 = 5.33$  kPa.

For peripheral venous blood this is likely to be true if the peripheral limb has a clearly recognizable arterial pulse, a normal capillary response, and a normal colour and temperature. For central or mixed venous blood this assumption is less likely to be true, as the different organ systems can add different and substantial amounts of acid into the blood circulation in situations with e.g. anaerobic metabolism. In addition it is assumed that the respiratory quotient, RQ, (i.e. the ratio of CO<sub>2</sub> production ( $\dot{V}\text{CO}_2$ )) and O<sub>2</sub> utilization ( $\dot{V}\text{O}_2$ )) over the tissue sampling site cannot vary outside the range 0.7 and 1.0. RQ of the tissue cells can only vary between 0.7 and 1.0, being 0.7 in aerobic metabolism of fat and 1.0 in aerobic metabolism of carbohydrate. Whilst R, the respiratory exchange ratio, measured at the mouth, may vary outside this range, the RQ over the tissue sampling site can only do so if there is a rapid flow of acid, base or CO<sub>2</sub> in or out of the tissues where the venous sampling occurs. This may occur for peripheral venous blood sampling in situations involving rapid disturbance of acid-base status, such as in exercise (Chuang et al. 1999). However, in a warm, well perfused extremity this rapid re-distribution is less likely. For central or mixed venous blood sampling RQ may vary in the same situations mentioned when describing the BE situation above.

This means that anaerobically sampled venous blood can be “arterialised” mathematically by simulating the removal/addition respectively of a constant ratio (RQ) of CO<sub>2</sub> and O<sub>2</sub> over the tissues. This simulation is then performed until the arterialised oxygen saturation matches the arterial oxygen saturation measured using a pulse oximeter. The details of this mathematical transformation now follow. This transformation is implemented as a Java computer program, which, when running on a PC with a 1.4 GHz Pentium M processor takes about one second to run.

**Step A:** First an anaerobic venous blood sample is drawn (figure 1) and measurements of pH<sub>v</sub>, PCO<sub>2,v</sub>, SO<sub>2,v</sub>, PO<sub>2,v</sub>, Hb<sub>v</sub>, Methaemoglobin (MetHb<sub>v</sub>), and carboxyhaemoglobin (COHb<sub>v</sub>) are taken to provide a picture of the acid/base and oxygenation status of the venous blood.

**Step B:** The venous measurements pH<sub>v</sub>, PCO<sub>2,v</sub>, PO<sub>2,v</sub>, SO<sub>2,v</sub>, Hb<sub>v</sub>, MetHb<sub>v</sub>, and COHb<sub>v</sub> are used to calculate the total CO<sub>2</sub> concentration (tCO<sub>2,v</sub>), total O<sub>2</sub> concentration (tO<sub>2,v</sub>), BE (BE<sub>v</sub>), and the concentration of 2,3 diphosphoglycerate (DPG<sub>v</sub>) in the venous blood. This can be performed using mathematical models of the acid base chemistry of blood (Siggaard-Andersen 1974). The method presented here uses the mathematical model of Rees and Andreassen (Rees & Andreassen 2005). It should be noted that BE is defined here as the concentration of strong acid necessary to titrate fully oxygenated blood to a pH<sub>p</sub> = 7.4, at a PCO<sub>2</sub> = 5.33 kPa. In the conventional definition (called Actual Base Excess (ABE) (Radiometer Medical A/S 1994)), BE is defined without fully oxygenating the blood (Rees & Andreassen 2005). Because of Bohr-Haldane effects ABE values therefore depend upon oxygen level and are not the same in arterial and venous blood even in the absence of addition of acid or base in

to the blood from the tissue. In the definition of BE used here values of BE are independent of  $O_2$  level (Rees & Andreassen 2005) and will only change if strong acids or bases are added.

In addition, if measurements of the venous plasma strong ions  $Na^+$ ,  $K^+$  and  $Cl^-$  are available these can be used to calculate the strong ion difference (SID) (Stewart 1983), the plasma non-bicarbonate buffer base ( $NBB_p^-$ ) and, in combination with  $pH_v$ , the total concentration of plasma non-bicarbonate buffer ( $tNBB_p$ ). Alternatively in the absence of measurements of strong ion concentrations,  $tNBB_p$  can be fixed to the normal value ( $tNBB_p = 23.5$  meq/l) (Rees & Andreassen 2005).

Calculation of arterial values requires a description of the oxygen binding to haemoglobin, more specifically the relationship between values of  $PO_2$  and  $SO_2$  in the blood, known as the oxygen dissociation curve (ODC). The ODC has been implemented using a sigmoidal functions, (Hill 1910; Siggaard-Andersen et al. 1984) the position of the ODC being shifted according to the pH,  $PCO_2$  and the amount of 2,3-diphosphoglycerate (DPG) in the blood. In the method presented here the ODC has been represented using the model of Siggaard-Andersen et al. (Siggaard-Andersen et al. 1984) modified for inclusion in Version 3 of the oxygen status algorithm (Siggaard-Andersen & Siggaard-Andersen 1995). DPG is calculated by finding the value of DPG for which the ODC passes through the measured venous  $PO_{2,v}$  and  $SO_{2,v}$  as illustrated in figure 2.

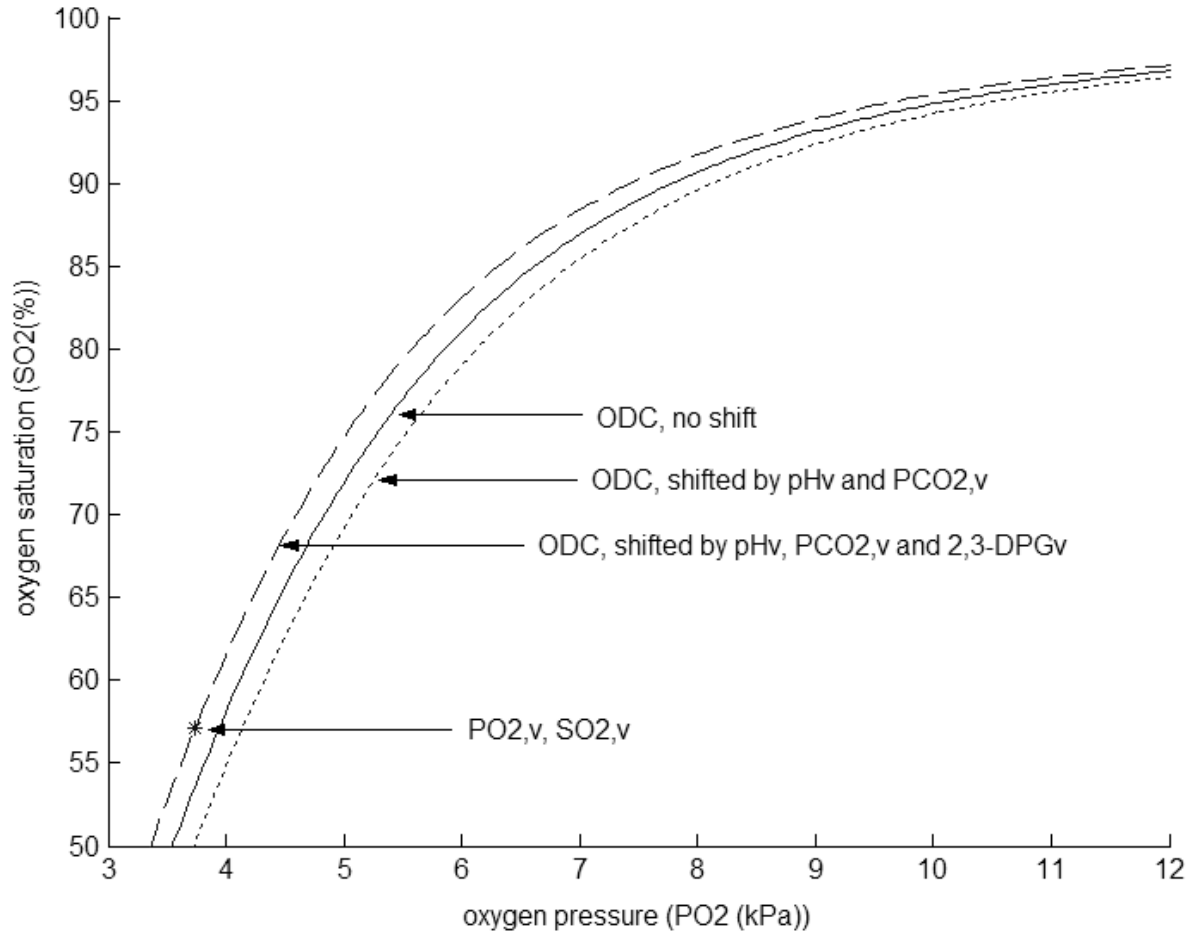


Figure 2 : For blood oxygen saturation ( $SO_2$ ) equal to 90%, DPG values can be estimated with a precision of 0.2 mmol/l (standard deviation) [22]. This precision improves at lower values of  $SO_2$ , as seen in the venous blood. (taken from Rees et al. 2006 with permission from Elsevier)

**Step C:** Using the variables describing venous blood ( $tCO_{2,v}$ ,  $tO_{2,v}$ ,  $Hb_v$ ,  $BE_v$ ,  $DPG_v$ ,  $tNBB_{p,v}$ ) calculation of the respective variables in arterial blood can now be performed. First, we assume that the concentration of haemoglobin, the total concentration of plasma non-bicarbonate buffer, and the concentration of 2-3 DPG are the same in arterial and venous blood, i.e.

$$DPG_a = DPG_v$$

$$Hb_a = Hb_v$$

$$tNBB_{p,a} = tNBB_{p,v}$$

If the tissues drained by the vein from which the venous blood sample is taken supply an amount of strong acid or base,  $\Delta BE_{av}$ , to the blood then

$$BE_a = BE_v + \Delta BE_{av}$$

Calculation of the total concentration of  $O_2$  and  $CO_2$  in arterial blood is then performed by simulating addition of a concentration of  $O_2$  ( $\Delta O_2$ ), to the venous blood and removing a concentration of  $CO_2$  ( $\Delta CO_2$ , where  $\Delta CO_2 = RQ \Delta O_2$ ) from the venous blood, i.e.

$$tO_{2,a} = tO_{2,v} + \Delta O_2$$

$$tCO_{2,a} = tCO_{2,v} - RQ \Delta O_2$$

**Step D:** Calculated values of arterialised blood  $tCO_{2,a}$ ,  $tO_{2,a}$ ,  $Hb_a$ ,  $BE_a$ ,  $tNBB_{p,a}$ , and  $DPG_a$  are then used to calculate the remaining variables describing arterialised blood, i.e.  $pH_a$ ,  $PCO_{2,a}$ ,  $PO_{2,a}$ , and  $SO_{2,a}$ , in a reverse of the process described in step B.

**Step E:** The calculated arterialised oxygen saturation  $SO_{2,a}$  is then compared with that measured by the pulse oximeter ( $SpO_2$ ), the difference between the two giving an error =  $SO_{2,a} - SpO_2$ . By varying the value of  $\Delta O_2$  and repeating steps C-E (figure 1), a value of  $\Delta O_2$  can be found for which the error is zero. At this point the  $\Delta O_2$  represents the concentration of  $O_2$  added, and  $RQ$  multiplied by  $\Delta O_2$  the concentration of  $CO_2$  removed, so as to transform venous to arterialised blood. For this value of  $\Delta O_2$ , calculated values of all variables describing arterialised blood ( $pH_a$ ,  $PCO_{2,a}$ ,  $PO_{2,a}$ , and  $SO_{2,a}$ ) should be equal to measured arterial values.

The method has been tested for sensitivity to measurement error, physiological assumptions and handling of the blood. The testing is based on a hypothetical patient with normal arterial and peripheral venous blood values ( $pH_v = 7.370$ ,  $PCO_{2,v} = 6.1$  kPa,  $PO_{2,v} = 5.5$  kPa,  $SO_{2,v} = 75$  %,  $tNBB_{pv} = 23.5$  meq/l,  $Hb_v = 9.3$  mmol/l,  $SO_{2,a} = SpO_2 = 97$  %,  $RQ = 0.82$ ), giving after application of the method 'arterialised' values of  $pH_a = 7.396$ ,  $PCO_{2,v} = 5.41$  kPa, and  $PO_{2,v} = 12.41$  kPa.

<i>Errors in calculated arterialised values</i>							
	pH <sub>a</sub>	PCO <sub>2,a</sub> (kPa)	PO <sub>2,a</sub> (kPa)	BE <sub>a</sub> (mmol/l)	SBE <sub>a</sub> (mmol/l)	SBC <sub>a</sub> (mmol/l)	DPG <sub>a</sub> (mmol/l)
<b>Venous measurement errors<sup>a</sup></b>							
pH <sub>v</sub> ± 0.006	± 0.006	± 0.00	± 0.00	± 0.44	± 0.45	± 0.40	± 0.09
PCO <sub>2,v</sub> ± 0.09 kPa	± 0.000	± 0.09	± 0.00	± 0.32	± 0.32	± 0.28	± 0.01
PO <sub>2,v</sub> ± 0.2 kPa	± 0.000	± 0.00	± 0.39	± 0.00	± 0.00	± 0.00	± 0.58
Hb <sub>v</sub> ± 0.3 mmol/l	± 0.000	± 0.02	± 0.01	± 0.05	± 0.04	± 0.05	± 0.00
SO <sub>2,v</sub> ± 0.5 %	± 0.001	± 0.02	± 0.10	± 0.02	± 0.02	± 0.01	± 0.15
<b>Pulse oximetry errors (± 2 %)</b>							
SpO <sub>2</sub> + 2%	+ 0.004	-0.09	+ 6.71	± 0.00	-0.06	0.00	0.00
SpO <sub>2</sub> - 2%	- 0.003	+ 0.07	- 2.16	± 0.00	0.05	0.00	0.00
<b>Physiological assumptions</b>							
ΔBE <sub>av</sub> ± 0.2 mmol/l	± 0.006	± 0.08	± 0.07	± 0.00	± 0.20	± 0.18	± 0.00
RQ ± 0.08	± 0.005	± 0.10	± 0.06	± 0.00	± 0.36	± 0.30	± 0.00

Table 1 : Sensitivity of calculated values of arterial acid-base status on measurement errors and physiological assumptions. Reference conditions: a hypothetical patient with normal arterial and peripheral venous blood values (pH<sub>v</sub> = 7.370, PCO<sub>2,v</sub> = 6.1 kPa, PO<sub>2,v</sub> = 5.5 kPa, SO<sub>2,v</sub> = 75 %, tNBB<sub>pv</sub> = 23.5 meq/l, Hb<sub>v</sub> = 9.3 mmol/l, SO<sub>2,a</sub> = SpO<sub>2</sub> = 97%, RQ = 0.82), giving after application of the method 'arterialised' values of pH<sub>a</sub> = 7.396, PCO<sub>2,v</sub> = 5.41 kPa, and PO<sub>2,v</sub> = 12.41 kPa. (taken from Rees et al. 2006 with permission from Elsevier)

Table 1 illustrates the sensitivity of the method to errors in the measurement of venous blood, pulse oximetry, and the physiological assumptions included in the method. The method is tested for errors in venous blood samples amounting to ±1 standard deviation of the usual measurement errors (Radiometer Medical A/S 1994). Errors in the measurement of pH<sub>v</sub>, PCO<sub>2,v</sub> and PO<sub>2,v</sub> translate into similar errors in calculated pH<sub>a</sub>, PCO<sub>2,a</sub> and PO<sub>2,a</sub>. The small error seen in calculated BE<sub>a</sub> is addressed in the test of the assumption of constant value of BE differences below and in the conclusion of this chapter. Errors in the measurement of Hb result in only small errors in the calculated PCO<sub>2,a</sub> and PO<sub>2,a</sub>. Errors in the measurement of SO<sub>2,v</sub> translate into an error in the calculated PO<sub>2,a</sub> = ± 0.1 kPa, with little error in the calculation of pH<sub>a</sub> and PCO<sub>2,a</sub>.

The method is tested for errors in pulse oximetry measurement of SpO<sub>2</sub> amounting to ± 2 % measurement error (Van de et al. 2001; Wouters et al. 2002). Errors in SpO<sub>2</sub> give very little error in the calculation of pH<sub>a</sub> and PCO<sub>2,a</sub>. An error in SpO<sub>2</sub> of 2 % in the range of SpO<sub>2</sub> from 97-95 % gives an error in the

calculated arterial  $PO_2$  of about 2 kPa. At values of  $SpO_2$  greater than 97 % the error in the calculation of arterial oxygen saturation becomes substantial. This is due to the flat shape of the oxygen dissociation curve at high levels of oxygen saturation, such that small changes in  $SO_2$  result in large changes in  $PO_2$ . Table 1 also illustrates the sensitivity of the method to the assumptions of constant values of  $RQ$  and  $\Delta BE_{av}$ . A BE difference between the venous and arterial blood of  $\pm 0.2$  mmol/l, or a variation of  $RQ \pm 0.08$  give only small errors in the calculation of  $pH_a$  ( $\leq 0.006$ ),  $PCO_{2,a}$  ( $\leq 0.10$  kPa) and  $PO_{2,a}$  ( $\leq 0.07$  kPa).

Errors can also occur due to poor handling of blood. These can have several causes: blood may separate into plasma and erythrocyte fractions; metabolism may continue in the blood cells; diffusion of  $O_2$  and  $CO_2$  may occur through plastic sampling syringes; and air bubbles may enter the blood. Errors due to the handling of blood can be minimised. For blood separation, the first 20 minutes results in about a 5 % separation of plasma (Hung et al. 1994) resulting in only a small change in haemoglobin concentration in the non-separated blood. Changes in  $PO_2$ ,  $PCO_2$  and  $pH$  due to cell metabolism are negligible if blood is placed on ice and analysed within a 30 minute period (Harsten et al. 1988; Hung et al. 1994; Nanji & Whitlow 1984). At room temperature significant changes in  $pH$ ,  $PCO_2$  and  $PO_2$  do not occur until between 10 and 20 minutes after sampling (Biswas et al. 1982; Nanji & Whitlow 1984). Changes in  $PCO_2$  and  $PO_2$  due to diffusion across plastic syringes have been shown to be small for durations as long as 5 hours (Wu et al. 1997). All these changes are therefore negligible for both arterial and calculated arterial values as long as blood is analysed within 10 minutes, or if placed on ice and measured within 30 minutes.

The sensitivity of the method to air bubbles is analyzed by performing simulations with the mathematical model of acid-base chemistry of Rees and Andreassen (Rees & Andreassen 2005) .



Bubble volume (% sample)	Venous blood				Arterial blood			
	$\Delta\text{pH}_v$	$\Delta\text{PCO}_{2,v}$ (kPa)	$\Delta\text{PO}_{2,v}$ (kPa)	$\Delta\text{SO}_{2,v}$ (%)	$\Delta\text{pH}_a$	$\Delta\text{PCO}_{2,a}$ (kPa)	$\Delta\text{PO}_{2,a}$ (kPa)	$\Delta\text{SO}_{2,a}$ (%)
5 % in arterial blood					0.002	-0.05	3.45	1.4
Calculated arterial values								
5 % in venous blood	-0.001	-0.01	0.41	3.6	0.009	0.45	-0.05	N/A

Table 2 : Simulated errors due to the effects of air bubbles on arterial and venous blood, and on calculated “arterialised” blood values. (taken from Rees et al. 2006 with permission from Elsevier)

Table 2 illustrates the results from simulating air bubbles ( $f\text{O}_2 = 0.21$ ,  $f\text{CO}_2 = 0$ ) of 5 % total volume equilibrated for  $\text{O}_2$  and  $\text{CO}_2$  pressure with arterial and venous blood. Venous blood values calculated in this way are subsequently “arterialised” using the venous to arterial conversion method.

In arterial and venous blood simulated bubbles gave negligible errors in pH and  $\text{PCO}_2$ . Bubbles have the greatest effect on oxygenation when the  $\text{PO}_2$  in the blood is furthest from the value in air and haemoglobin is not fully saturated with oxygen. For arterial blood a 5 % bubble equilibrated with blood at  $\text{SO}_{2,a} = 97\%$  causes an error in  $\text{PO}_{2,a} = 3.45$  kPa and  $\text{SO}_{2,a} = 1.4\%$ . For venous blood, where haemoglobin is not completely saturated with oxygen, changes in oxygen saturation caused by air bubbles are greater than arterial blood, whilst changes in oxygen pressure are less. For arterialised values calculated from venous blood including bubbles, errors in  $\text{pH}_a$  and  $\text{PCO}_{2,a}$  are higher than those for direct sampling of arterial blood including bubbles. For  $\text{PO}_{2,a}$  the error in the calculated arterial value is less than that in the directly measured arterial blood with air bubbles.

## Conclusion

This theoretical analysis of the sensitivity of the method to assumptions and possible measurement errors was used to plan further studies. When testing the sensitivity to assumptions, the critical assumptions are that the difference between the acid–base chemistry in arterial and peripheral venous blood sampled from well-perfused, warm tissue is primarily due to the aerobic metabolism in that tissue, meaning that the RQ over the sampling site would be between 0.7 and 1.0 and the change in BE between arterial and venous blood would approximate zero. Fortunately, the quality of perfusion of a limb, and hence the degree of anaerobic metabolism, can be simply assessed in the clinic, meaning that situations resulting in large BE differences between the arterial and venous blood should be easily identified. These situations include

acute changes in acid–base status or peripheral perfusion such as acute hypovolaemic shock, where the method may not be useful.

Waldau et al. have shown that R (the respiratory exchange ratio) has a mean and standard deviation of  $0.82 \pm 0.08$  for patients with sepsis. The method is relatively insensitive to changes in RQ of 0.08, resulting in errors in the calculated  $pH_a$ ,  $PCO_{2,a}$ , and  $PO_{2,a}$  of 0.005, 0.10 and 0.06 kPa, respectively. Similarly, the method has been shown to be insensitive to differences in BE across the sampling site ( $BE_{av}$ ) of 0.2 mmol/l, these errors giving errors in the calculated  $pH_a$  of 0.006, and  $PCO_{2,a}$  of 0.08 kPa, and very little error in the calculated  $PO_{2,a}$ . Indeed, the maximal errors in  $BE_{av}$  which give errors in  $pH_a$ ,  $PCO_{2,a}$ , and  $PO_{2,a}$  within the laboratory guidelines (CLIA-related publications) are about 6.5 times those associated with  $BE_{av} = 0.2$  mmol/l. This means that values of  $BE_{av}$  as high as  $6.5 \times 0.2 = 1.3$  mmol/l will still result in calculated arterialised values with errors within laboratory guidelines.

The method was also tested for its sensitivity to possible measurement errors in venous blood and pulse oximetry, and errors due to poor sampling or handling of the blood. Errors in calculated arterial values due to measurement error in the venous blood are relatively insignificant. Errors in calculated values of  $pH_a$ ,  $PCO_{2,a}$ , and  $PO_{2,a}$  are almost the same as those which would be obtained by direct measurement of arterial blood. Errors in pulse oximetry measurement of  $SpO_2$  have a standard deviation 2 %, at least for  $SpO_2$  values greater than 90 % where individual outliers do not exist (Van de Louw et al. 2001). Errors in calculated values of  $pH_a$  of 0.004 and  $PCO_{2,a}$  of 0.09 kPa, due to error of 2 % in  $SpO_2$  are small, and would remain insignificant even for errors in  $SpO_2$  three times this size. Calculation of arterial pH and  $PCO_2$  is therefore extremely insensitive to errors in  $SpO_2$ . The error in calculated  $PO_{2,a}$  depends on the oxygen level. For  $SO_{2,a}$  values  $\geq 97$  %, errors in calculated  $PO_{2,a}$  are large due to the flat shape of the ODC. For  $SO_{2,a}$  values  $< 97$  % errors of  $SpO_2$  of 2 % have less effect on the calculation of  $PO_{2,a}$  with an error in calculated  $PO_{2,a}$  of 2 kPa when  $SpO_2$  is varied from 97% to 95 %.

Errors due to the handling of blood can be minimised. For blood separation, the first 20 min results in about a 5 % separation of plasma (Hung et al. 1994) resulting in only a small change in haemoglobin concentration in the non-separated blood. Changes in  $PO_2$ ,  $PCO_2$ , and pH due to cell metabolism are negligible if blood is placed on ice and analysed within a 30 min period (Hung et al. 1984; Nanji & Whitlow 1984; Harsten et al. 1988). At room temperature significant changes in pH,  $PCO_2$ , and  $PO_2$  do not occur until between 10 and 20 min after sampling (Biswas et al. 1982; Nanji & Whitlow 1984). Changes in  $PCO_2$  and  $PO_2$  due to diffusion across plastic syringes have been shown to be small for durations as long as 5h (Wu et al. 1997). All these changes are, therefore, negligible for both arterial and calculated arterial values as long as blood is analysed within 10 min, or if placed on ice and measured with 30 min.

Calculated errors due to 5% air bubbles present in the venous blood give errors in calculated  $pH_a$  and  $PCO_{2,a}$  of 0.009 and 0.45 kPa respectively, meaning that some care should be taken to eliminate bubbles

from the venous blood sample. However, errors in calculated  $PO_{2,a}$  due to bubbles are less than those for directly sampled arterial blood containing bubbles. In the method presented here, venous samples must be taken anaerobically.

The method presented here is simple, requires no warming of the sampling site, and uses only standard equipment to measure blood gasses, a pulse oximeter and a computer for performing the calculations.

## Chapter 2

In this chapter the patient study will be described. The measured values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from venous and arterial blood will be compared to explore the possible clinical value of using venous blood to estimate arterial blood gas values. The chapter is based on article number II.

### Patient material

Arterial and venous blood samples were collected from 112 patients, with or without mechanical ventilation, median age 66 years, (range 26 – 81 years), 39 females. To ensure a broad range of acid-base and oxygenation status, patients were included from three different departments (pulmonary medicine, thoracic intensive care and multidisciplinary intensive care) of Aalborg Hospital, Denmark, and selected from three different groups, as follows:

1. Thirty-six haemodynamically stable patients diagnosed as having chronic obstructive pulmonary disease (COLD).
2. Fifty-one haemodynamically stable patients (defined as administration of inotropic medicine equivalent to a dose of dopamine  $\leq 5$  mg/kg/min) without COLD.
3. Twenty-five haemodynamically unstable patients without COLD.

The three departments allowed us to study a broad spectrum of diseases, many of them typical for an emergency department, that is, respiratory insufficiency, sepsis, pneumonia and trauma.

### Data acquisition.

For each patient an arterial and a peripheral venous blood sample were taken simultaneously, i.e. within 10 seconds. For patients with indwelling central venous or pulmonary artery catheters, venous blood samples were taken from these immediately after. An additional arterial blood sample was taken in patients having venous blood sampled from more than one sampling site immediately following sampling from all venous sites. Values of arterial blood (pH, PCO<sub>2</sub>, PO<sub>2</sub>) measured in the two arterial samples were compared to ensure that the patient had stable values of arterial acid-base and oxygenation status during the study.

All blood samples were taken anaerobically (PICO, Radiometer) and analysed for acid-base and oxygenation (ABL Radiometer). Arterial blood samples were taken from an arterial catheter or by puncture of the arteria radialis. Peripheral venous blood samples were taken from an upper extremity considered to be well perfused with normal temperature, capillary response and no apparent lesions.

The quality of blood samples was assessed by comparing measured values of haemoglobin in the arterial and venous blood. Differences between arterial and venous haemoglobin values greater than 0.5 mmol/l were considered to indicate sampling and/or handling error and the patient's data were excluded. This

meant exclusion of data from five patients. Three patients were excluded because of missed arterial or peripheral venous blood samples. A further patient was excluded as inspired oxygen fraction was increased during the sampling process.

The resulting study population was 31 patients in group 1 (COLD), 49 in group 2 (stable) and 23 in group 3 (unstable).

Of the total 103 patients with simultaneously taken arterial and peripheral venous blood samples, 73 had a central venous blood sample and 18 of them also had a mixed venous blood sample.

Ethical approval for the study was obtained from the Ethics Committee of North Jutland and Viborg Counties. Informed written and oral consent was obtained from the patient or legal guardian in all cases.

### **Statistical analysis**

Measured values of arterial and venous blood (peripheral, central and mixed) pH, PCO<sub>2</sub>, and PO<sub>2</sub> are compared. Correlation between arterial and venous values is described using Bland-Altman plots and statistics describing the mean difference (bias) and standard deviation (SD). Values of other acid-base parameters (BE, total buffer base, standard bicarbonate, etc.) can be calculated from measurements of pH, PCO<sub>2</sub>, PO<sub>2</sub> and haemoglobin in blood. Calculation of the arteriovenous differences of these parameters is not performed here.

### **Results**

Measured values of arterial, peripheral, central and mixed venous blood pH, PCO<sub>2</sub> and PO<sub>2</sub> for the three patient groups are shown in table 3.

		COLD (n=31)			Stable (n=49)				Unstable (n=23)			
		art	pv	cv	art	Pv	cv	mv	art	pv	cv	mv
pH	minimum	7.313	7.300	7.293	7.259	7.240	7.233	7.268	7.243	7.229	7.209	7.318
	25 % quartile	7.386	7.364	7.306	7.352	7.306	7.322	7.294	7.346	7.328	7.303	7.334
	median	7.408	7.388	7.365	7.375	7.349	7.345	7.322	7.402	7.369	7.330	7.391
	75 % quartile	7.457	7.423	7.375	7.414	7.389	7.375	7.356	7.425	7.404	7.378	7.412
	maximum	7.538	7.522	7.436	7.477	7.453	7.424	7.394	7.496	7.516	7.446	7.460
PCO <sub>2</sub>	minimum	4.95	5.10	6.22	4.03	4.61	4.93	5.51	3.98	4.31	4.64	4.49
	25 % quartile	5.85	6.34	6.28	5.03	5.50	5.84	5.90	4.55	5.27	5.60	5.18
	median	6.67	7.39	7.46	5.49	6.13	6.15	6.04	5.23	5.61	6.22	5.73
	75 % quartile	8.72	9.60	9.69	5.86	6.71	6.66	6.74	5.78	6.02	6.57	6.22
	maximum	10.81	12.65	10.90	6.85	7.60	7.81	6.98	7.15	6.49	7.44	6.36
PO <sub>2</sub>	minimum	6.61	2.78	5.07	8.75	2.03	3.86	3.58	9.19	3.73	3.90	3.28
	25 % quartile	8.97	4.36	5.89	11.30	4.05	4.42	4.40	11.05	6.07	4.52	3.75
	median	9.58	6.46	6.17	12.90	5.70	4.80	4.81	11.50	6.95	5.24	3.97
	75 % quartile	10.35	8.06	6.27	15.20	7.23	5.19	5.22	13.90	7.76	5.73	4.56
	maximum	12.70	9.60	6.49	28.30	10.80	6.97	5.97	21.3	12.10	7.16	4.88

Table 3 : Measured values of arterial, peripheral, central and mixed venous blood pH, PCO<sub>2</sub> and PO<sub>2</sub> for the three different groups, COLD, stable and unstable. Median, quartiles and extremes are shown. art : arterial blood; pv : peripheral venous blood; cv : central venous blood; mv : mixed venous blood  
(taken from Toftegaard et al. 2008 with permission from Ovid)

To further describe group 2 and 3 hemodynamically, values of lactate were measured. Group 2 (haemodynamically stable) had an arterial lactate of  $1.21 \pm 0.42$  mmol/l (mean  $\pm$  SD) and a peripheral venous lactate of  $1.46 \pm 0.42$  mmol/l. Group 3 (haemodynamically unstable) had an arterial lactate of  $1.64 \pm 0.63$  mmol/l (mean  $\pm$  SD) and a peripheral venous lactate of  $1.89 \pm 0.72$  mmol/l.

For the 73 patients with venous blood sampled from more than one site, the two arterial blood samples, taken before and after the venous samples, showed a difference of pH =  $0.0007 \pm 0.0137$  (mean  $\pm$  SD), pCO<sub>2</sub> =  $-0.02$  kPa  $\pm$   $0.22$  kPa, PO<sub>2</sub> =  $0.18$  kPa  $\pm$   $1.49$  kPa. These values were not considered to be clinically different, illustrating that these patients had stable acid-base and oxygenation status during the study.

In addition, for the same 73 patients peripheral and central venous blood were compared using Bland-Altman plots as illustrated in figure 3.

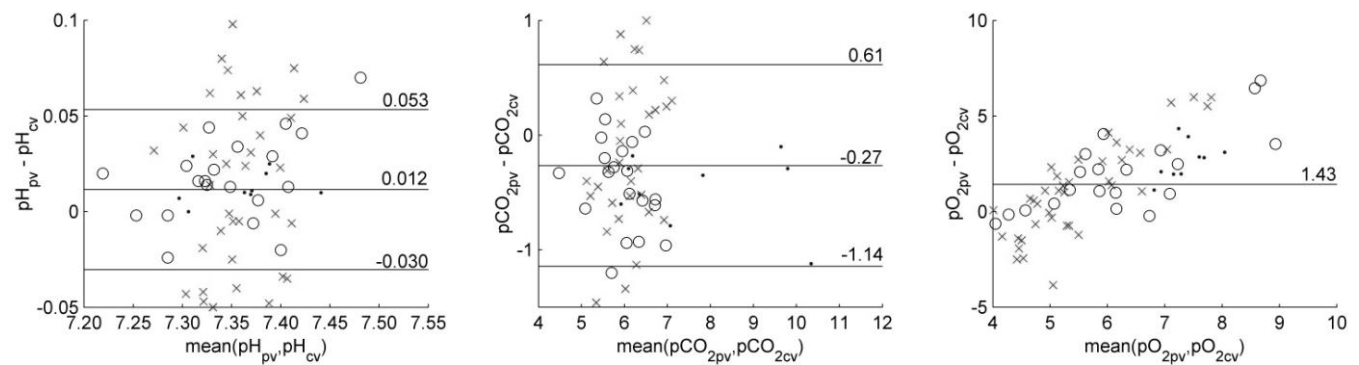


Figure 3 : Bland-Altman plots comparing measured peripheral venous and central venous values of pH, PCO<sub>2</sub> and PO<sub>2</sub>. n=73. For pH, PCO<sub>2</sub> and PO<sub>2</sub> bias are shown. For pH and PCO<sub>2</sub> 95 % limits of agreement ( $\pm$  2SD) are shown. For pH the SD was 0.021 and for PCO<sub>2</sub> SD was 0.45 kPa.

• = COLD patients; x = haemodynamically stable patients without COLD; o = haemodynamically unstable patients without COLD. (taken from Toftegaard et al. 2008 with permission from Ovid)

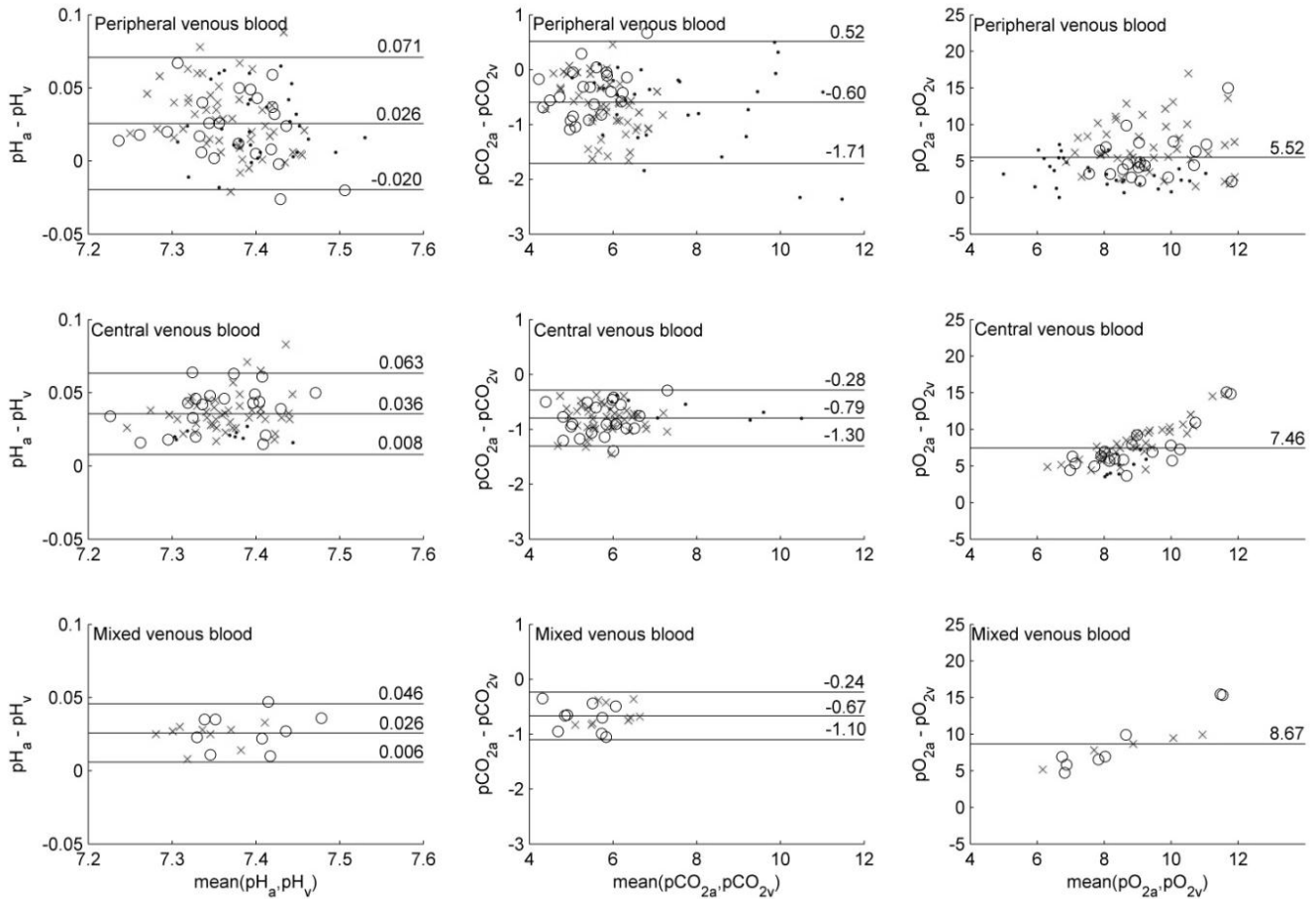


Figure 4 : Bland-Altman plots comparing measured arterial and venous values of pH, PCO<sub>2</sub> and PO<sub>2</sub> in peripheral, central and mixed venous blood. For pH and PCO<sub>2</sub> bias and 95 % limits of agreement ( $\pm$  2SD) are shown. For pH (peripheral, central and mixed venous blood) SD was 0.023, 0.014 and 0.010 respectively. For PCO<sub>2</sub> (peripheral, central and mixed venous blood) SD was 0.57 kPa, 0.26 kPa and 0.22 kPa respectively. Bias values for PO<sub>2</sub> are calculated for 4 kPa  $\leq$  PO<sub>2</sub>  $\leq$  12 kPa. n=103.

• = COLD patients; x = haemodynamically stable patients without COLD; o = haemodynamically unstable patients without COLD. (taken from Toftegaard et al. 2008 with permission from Ovid)

Figure 4 illustrates Bland-Altman plots comparing measured arterial and venous values of pH, PCO<sub>2</sub> and PO<sub>2</sub>. For pH and PCO<sub>2</sub> the difference between arterial and venous values is randomly distributed across the range of possible values, regardless of the venous sampling site. For PO<sub>2</sub>, a systematic increase in the difference between arterial and venous PO<sub>2</sub> can be seen with increasing PO<sub>2</sub> values. For pH and PCO<sub>2</sub>, where the arteriovenous difference is randomly distributed, the bias and SD describing the difference between arterial and venous values are given in figure 4 and table 4.



	pH	PCO <sub>2</sub> (kPa)
± 2 SD of Arterial - Peripheral Venous (n=103)	0.026 ± 0.046	-0.60 ± 1.13
± 2 SD of Arterial - Central Venous (n=73)	0.036 ± 0.028	-0.79 ± 0.52
± 2 SD of Arterial - Mixed Venous (n=18)	0.026 ± 0.020	-0.67 ± 0.44
Laboratory acceptable performance criteria (acceptable range)	± 0.04	± 0.67 <sup>a</sup>

Table 4: Bias ± 2 SD for the difference between arterial and venous blood, ± 2 SD compared to laboratory performance guidelines. It is assumed that these guidelines are comparable to a 95% confidence interval given by 2 SD. <sup>a</sup>Original value given as ± 5 mmHg. (taken from Toftegaard et al. 2008 with permission from Ovid)

Despite its skewed distribution a similar bias ± SD have been calculated for the difference between arterial and venous PO<sub>2</sub> of 6.27 ± 4.36 kPa(peripheral), 8.33 ± 3.74 kPa(central) and 11.00 ± 4.87 kPa(mixed) respectively. This bias ± SD is reduced for lower values of PO<sub>2</sub>, giving for PO<sub>2</sub> values ≤ 12 kPa 5.51 ± 3.38 kPa(peripheral), 7.46 ± 2.68 kPa(central) and 8.67 ± 3.43 kPa(mixed) respectively.

## **Discussion**

In this part of the thesis the direct-measured values of pH, PCO<sub>2</sub> and PO<sub>2</sub> in peripheral, central and mixed venous blood have been compared to simultaneously taken arterial blood values.

Simultaneous blood sampling was assured by testing for steady state during the sampling time.

In general, results are similar to those found previously in studies using venous blood sampled from a single site (Adroque et al. 1989; Brandenburg & Dire 1998; Brandi et al. 1995; Gambino 1959; Gennis et al. 1985; Gokel et al. 2000; Harrison et al. 1997; Kelly et al. 2001; Rang et al. 2002; Sutton et al. 1967; Weil et al. 1986; Yildizdas et al. 2004), or multiple sites in paediatric patients (Yildizdas et al. 2004).

Bland-Altman plots have been used to visualise and compare the results reporting mean difference (bias) and standard deviations (figure 4, table 4). The bias between arterial and venous values represents a necessary correction for converting venous values to arterial values and two standard deviations represents the error within which corrected values could reproduce the corresponding arterial values in 95% of cases. This correction can be expressed as:

$$pH_a = pH_v + \text{bias}_{pH} \pm 2SD$$

$$pCO_2 = pCO_{2v} + \text{bias}_{pCO_2} \pm 2SD$$

Ideally, this difference should be compared against clinical guidelines for acceptable precision of arterial measurements. To the best of our knowledge no such guidelines exist. Instead, table 4 illustrates these errors (± 2 SD) and acceptable laboratory performance criteria for measured arterial pH and PCO<sub>2</sub> (Burtis

& Ashwood 1999; Department of Health and Human Services 1998). It should, however, be recognised that laboratory criteria specify the precision with which the blood gas analyser ought to function, which is well within the necessary clinical precision. The results (table 4) show that venous values of pH, corrected for bias, can give arterial values which are within or close to laboratory acceptable performance criteria. This is also true for PCO<sub>2</sub>, except for peripheral venous blood, which gives a bias and standard deviation of -0.60 kPa  $\pm$  1.14 kPa ( $\pm$  2 SD), outside acceptable laboratory performance criteria, but within reasonable clinical acceptance criteria for classifying respiratory abnormalities. For PO<sub>2</sub> values of bias are not randomly distributed and even for PO<sub>2</sub>  $\leq$  12 kPa a bias  $\pm$  SD of 5.51  $\pm$  3.38 kPa for peripheral venous blood is clearly outside both laboratory and reasonable clinical acceptance criteria.

In addition peripheral and central venous values of pH, PCO<sub>2</sub> and PO<sub>2</sub> have been compared, showing a clear correlation between values of pH with a bias and standard deviation of 0.012  $\pm$  0.042 ( $\pm$  2 SD) and hence potential for peripheral venous blood pH to be used to estimate central venous values. The correlation between values of PCO<sub>2</sub> is poorer, but peripheral PCO<sub>2</sub> may still be a useful estimate of central venous values. Peripheral venous PO<sub>2</sub> can clearly not estimate central venous values.

The haemodynamic stable group (group 2) was described in terms of none or a small dose of inotropic medication (equivalent to  $\leq$  dopamine (5 mg/kg/min)) and the unstable group (group 3) received inotropic medication (equivalent to  $>$  dopamine (5 mg/kg/min)), in principle norepinephrine. The values of lactate were measured in the study, and the results indicate that there was but a small difference between groups 2 and 3.

## Conclusion

This part of the thesis has evaluated the use of venous blood from three different sampling sites in evaluating acid–base and oxygenation status in different patient groups.

The results show that venous values of pH, corrected for bias, can give arterial values, which are within or close to laboratory acceptable performance criteria. This is also true for

PCO<sub>2</sub>, except for peripheral venous blood. For PO<sub>2</sub> bias is not randomly distributed and for peripheral venous blood the bias and SD are clearly outside both laboratory and reasonable clinical acceptance criteria.

Peripheral and central venous values of pH, PCO<sub>2</sub> and PO<sub>2</sub> have been compared, showing a clear correlation between values of pH, a weaker correlation between values of PCO<sub>2</sub> and no correlation between values of PO<sub>2</sub>.

The results have indicated the need to develop a method for correction of the venous values to more accurate “arterial” values, before the venous blood could be used as a primary screening tool or as a monitoring tool to avoid or delay arterial punctures.

### **Chapter 3**

In this chapter the method for converting venous to arterial values will be evaluated on the patient population described in section 2. The chapter is based on article number III.

The blood gas values from the venous blood samples taken from the resulting 103 evaluable patients are converted to arterial values using the venous to arterial conversion method described in chapter 1. The peripheral arterial oxygen saturation was measured by a pulse oximeter (COSMO plus, Novamatrix Medical Systems, Wallingford, Connecticut).

RQ is selected to be 0.82 (Waldau et al. 2002) and  $\Delta BE_{av}$  is set to zero.

#### **Statistical analysis**

Calculated arterial values of pH,  $PCO_2$  and  $PO_2$  are compared with the simultaneously measured arterial values using Bland Altman plots. Values of bias and standard deviation between measured and calculated arterial values are reported. This comparison is performed for arterial values calculated from peripheral venous, central venous and mixed venous values respectively. Comparison of the mean difference between calculated and measured arterial values are analysed for the three different patient groups and the three different venous sampling sites using one-sided ANOVA.

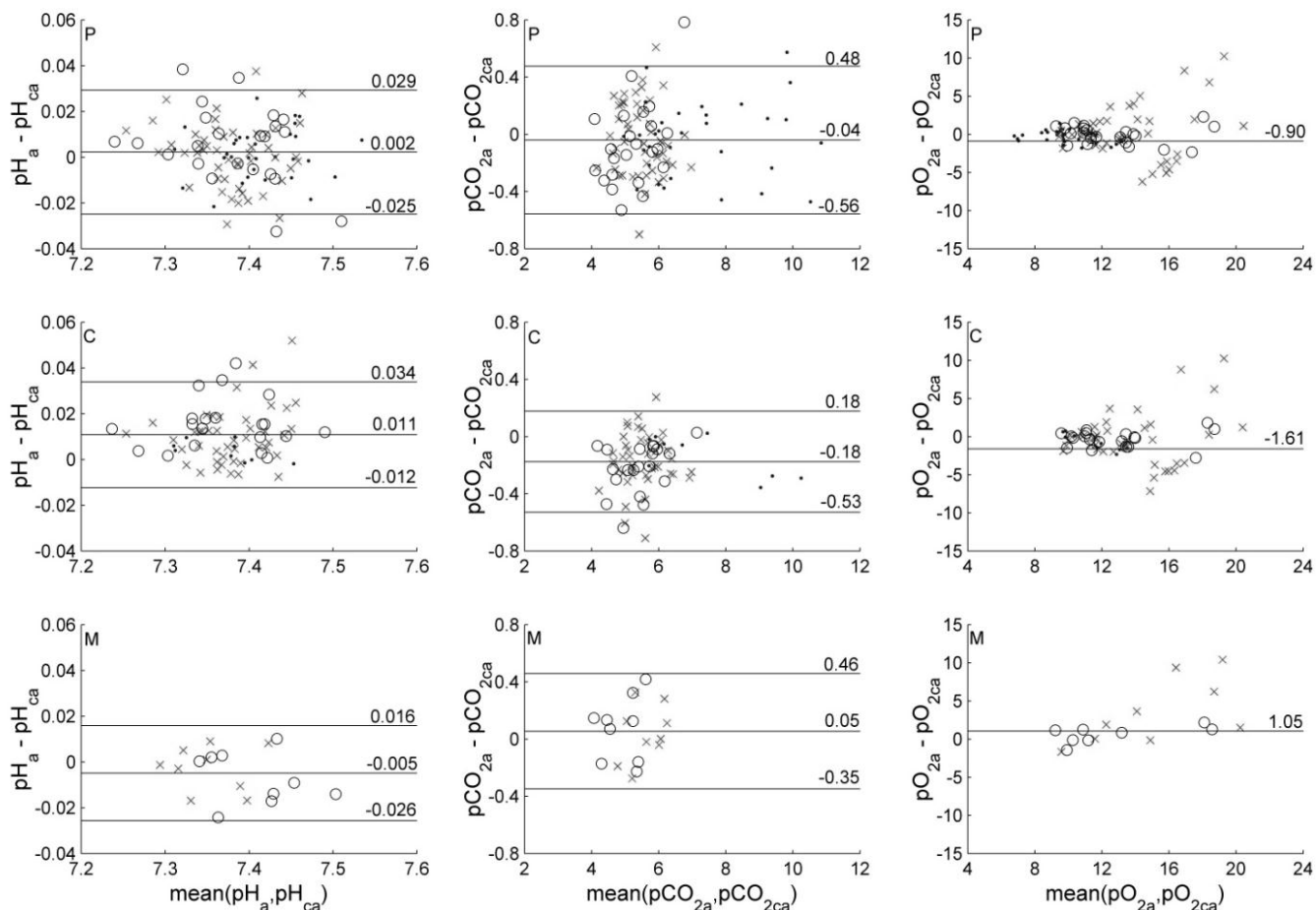


Figure 5: Bland-Altman plots comparing measured arterial (a) and calculated arterial (ca) values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from peripheral (P), central (C) and mixed venous (M) blood. Bias and 95 % limits of agreement (± 2SD) are shown for pH and PCO<sub>2</sub>. For pH (peripheral, central and mixed venous blood) SD was 0.014, 0.012 and 0.011 respectively. For PCO<sub>2</sub> (peripheral, central and mixed venous blood) SD was 0.26 kPa, 0.18 kPa and 0.21 kPa respectively. • = COLD patients; x = haemodynamically stable patients without COLD; o = haemodynamically unstable patients without COLD. (taken from Toftegaard et al. 2009 with permission from BMJ)

			SpO <sub>2</sub> ≤ 96%	SpO <sub>2</sub> ≤ 97%
	pH	PCO <sub>2</sub> (kPa)	PO <sub>2</sub> (kPa)	PO <sub>2</sub> (kPa)
Arterial – calculated arterial values from peripheral venous blood (n=103)	0.002 ± 0.027	-0.04 ± 0.52	0.21 ± 1.85 (n=41)	0.40 ± 3.32 (n=63)
Arterial – calculated arterial values from central venous blood (n=73)	0.011 ± 0.023	-0.18 ± 0.35	0.39 ± 1.97 (n=18)	0.28 ± 3.88 (n=35)
Arterial – calculated arterial values from mixed venous blood (n=18)	-0.005 ± 0.021	0.06 ± 0.40	0.53 ± 1.54 (n=1)	1.40 ± 6.43 (n=10)
Laboratory acceptable performance criteria (acceptable range)	± 0.04	± 0.67 <sup>a</sup>	± 0.6 <sup>b</sup>	± 0.6 <sup>b</sup>
Arterial – arterial variability	± 0.027	± 0.45	± 1.48	± 1.67

Table 5: Bias ± 2SD for the difference between arterial and calculated arterial blood values from venous blood taken from the 3 sampling sites, compared to laboratory performance guidelines.

It is assumed that these guidelines are comparable to a 95% confidence interval given by 2 SD. <sup>a</sup>Original value given as ± 5 mmHg. <sup>b</sup>Original value given as ± 3 SD of measurement equipment error, where one SD is assumed to be 0.2 kPa according to Radiometer Medical A/S 1994. (Modified from Toftegaard et al. 2009 with permission from BMJ)

## Results

Figure 5 and table 5 illustrate the difference between measured arterial values and calculated arterial values using the venous to arterial conversion method, for peripheral, central and mixed venous blood.

Calculated values of arterial pH and PCO<sub>2</sub> have very small bias and standard deviations regardless of the venous sampling site. In all cases these errors are within those considered acceptable for the performance of laboratory equipment (table 5) (Burtis & Ashwood 1999; Department of Health and Human Services 1998) and well within the limits of error acceptable in clinical practice. In addition the SD of calculated values of pH and PCO<sub>2</sub> given in table 5 are similar to the variability between arterial samples in the 73 patients where two arterial samples were taken. For pH and PCO<sub>2</sub> the variability between arterial samples were 0.027 (2SD) and 0.45 kPa (2SD) respectively.

For PO<sub>2</sub> the situation is more complex. The error in calculated PO<sub>2</sub> values has a standard deviation which is dependent upon the PO<sub>2</sub> level, with higher values of calculated PO<sub>2</sub> associated with more calculation error. This is also true for the variability between arterial samples, 1.48 (2SD) for SpO<sub>2</sub> ≤ 96 % and 1.67 (2SD) for SpO<sub>2</sub> ≤ 97 %. Table 5 illustrates this with bias and standard deviation reported for PO<sub>2</sub> values corresponding to SpO<sub>2</sub> ≤ 96 % and SpO<sub>2</sub> ≤ 97 %. Errors are outside those considered acceptable for the performance of laboratory equipment, but for SpO<sub>2</sub> ≤ 96 % the error in PO<sub>2</sub> of 1.85 kPa (2SD) is similar to the variability between arterial samples, and the calculated value may therefore still be useful in clinical practice.

		pH		PCO <sub>2</sub> (kPa)	
	N				
Peripheral venous blood					
All patients	103	0.002 ± 0.027		-0.04 ± 0.52	
Group I	31	0.002 ± 0.022	p = 0.45 (ns)	-0.03 ± 0.52	p = 0.81 (ns)
Group II	49	0.001 ± 0.027		-0.03 ± 0.50	
Group III	23	0.005 ± 0.033		-0.07 ± 0.57	
Central venous blood					
All patients	73	0.011 ± 0.023		-0.18 ± 0.35	
Group I	9	0.004 ± 0.009	p = 0.03 (s)	-0.14 ± 0.28	p = 0.41 (ns)
Group II	44	0.010 ± 0.024		-0.16 ± 0.37	
Group III	20	0.016 ± 0.022		-0.22 ± 0.34	
Mixed venous blood					
All patients	18	-0.005 ± 0.021		0.06 ± 0.40	
Group I	0		p = 0.41 (ns)		p = 0.71 (ns)
Group II	9	-0.003 ± 0.020		0.04 ± 0.39	
Group III	9	-0.007 ± 0.022		0.07 ± 0.44	

Table 6: Comparison between the 3 groups expressed by bias ± 2SD for the difference between arterial and calculated arterial blood gas values from venous blood taken from the 3 sampling sites. The groups are compared using one-sided ANOVA. Group I: COLD. Group II: Hemodynamically stable. Group III: Hemodynamically unstable. (modified from Toftegaard et al. 2009 with permission from BMJ)

Table 6 illustrates the difference between measured arterial and calculated arterial values of pH and PCO<sub>2</sub>, subdivided to each of the patient groups. The same comparison for PO<sub>2</sub> is omitted due to the non-random distribution of errors for PO<sub>2</sub>. Errors in the calculation of arterial pH and PCO<sub>2</sub> were not significantly different between the patient groups, regardless of sampling site, except for pH sampled from the central vein where there was a significant difference in calculated pH values between groups I and III (p=0.03).

		pH		PCO <sub>2</sub> (kPa)	
	N				
Peripheral blood	103	0.002 ± 0.027	p < 0.05 (s)	-0.04 ± 0.52	p < 0.05 (s)
Central venous blood	73	0.011 ± 0.023		-0.18 ± 0.35	
Mixed venous blood	18	-0.005 ± 0.021		0.06 ± 0.40	

Table 7: Comparison between the 3 sampling sites expressed by bias ± 2SD for the difference between arterial and calculated arterial blood gas values from venous blood. The sampling sites are compared using one-sided ANOVA. (modified from Toftegaard et al. 2009 with permission from BMJ)

Table 7 illustrates the difference between measured and calculated arterial values of pH and PCO<sub>2</sub>, subdivided by sampling site. Calculated values of pH and PCO<sub>2</sub> are significantly different across the sampling sites. (p<0.05). In particular the accuracy of pH and PCO<sub>2</sub> calculations made from peripheral venous blood was significantly better than those from central venous blood (p<0.005, for both pH and PCO<sub>2</sub>). Comparison of the accuracy in calculations made from peripheral and mixed venous blood did not show statistical significance.

### Discussion and conclusions of the adult study

When compared to measured arterial values of pH and PCO<sub>2</sub>, calculated values have a precision within laboratory acceptable performance criteria and similar to the variability between consecutive arterial blood samples. This is true for venous blood sampled from peripheral veins, central veins or the pulmonary artery and for patients with different respiratory and hemodynamic status. Arterial values of pH and PCO<sub>2</sub> calculated from peripheral venous blood are significantly more precise than those calculated from central venous blood. This may seem surprising giving the clinical acceptance of central or mixed venous blood in the evaluation of patients' acid-base status. This can be explained by the selection of the sampling site. Peripheral venous blood sampled from a well perfused extremity is unlikely to have large metabolic disturbances meaning that the BE of arterial and peripheral venous blood is likely to be similar, but this may not be true for the comparison between arterial and either central or mixed venous blood, which include blood from different organs with different metabolic status.

For SpO<sub>2</sub> values less than or equal to 96 % the venous to arterial conversion method can calculate PO<sub>2</sub> with a SD of 0.93 kPa, which may be useful in clinical practice (table 5) and is similar to the variability between consecutive arterial blood samples of 0.74 kPa seen in these data. For SpO<sub>2</sub> values greater than 96 % PO<sub>2</sub> values can not be predicted within an acceptable clinical range. This is due to the flat shape of the ODC at high levels of SO<sub>2</sub>, meaning that small changes in SO<sub>2</sub> result in large changes in PO<sub>2</sub>.

Patients with low values of SpO<sub>2</sub> are clinically the most interesting and it is therefore encouraging that calculations of PO<sub>2</sub> are most precise at low levels. The imprecision of PO<sub>2</sub> calculations at values of SpO<sub>2</sub>

greater than 96 % might however be seen as a limiting factor the utility of the method in calculating  $PO_2$  in undifferentiated patients receiving supplementary oxygen. Direct measurement of arterial  $PO_2$  in these patients would not however provide substantial extra information about the status of the patient's lungs, unless the relationship between inspiratory and arterial oxygen can be determined. In these patients it is typical that supplementary oxygen is delivered nasally meaning that inspired oxygen levels cannot be determined precisely.

Using the method described here can be seen as a significant improvement over direct comparison letting venous values substitute for arterial values. For peripheral venous blood the precision of calculated arterial values are 0.027 (2SD) for pH and 0.52 kPa (2SD) for  $PCO_2$ . For pH and  $PCO_2$  these SD's are half that seen for direct comparison between measured arterial and venous blood (Toftegaard et al. 2008), illustrating that the venous to arterial conversion method improves substantially the information obtained from peripheral venous blood.

More important the results show that the SD of calculated values of pH,  $PCO_2$  and  $PO_2$  (for  $SpO_2 \leq 96\%$ ) are similar to the variability between consecutive arterial samples.

This method assumes that, for a peripheral limb with a clearly recognisable pulse and a normal capillary response, the amount of acid added to the blood as it passes the tissues is small. The method also assumes that a fixed value of RQ can be used in the calculation. In addition the method has been shown, using sensitivity analysis, to be insensitive to errors in the measurement of venous blood, and to the effects of bubbles (Rees et al. 2006). These assumptions seem justified given the accuracy and precision with which the method can calculate arterial values in this heterogeneous patient group.

The method has however been shown previously, using sensitivity analysis, to be sensitive to errors in  $SpO_2$  when calculating arterial  $PO_2$  (Rees et al. 2006).



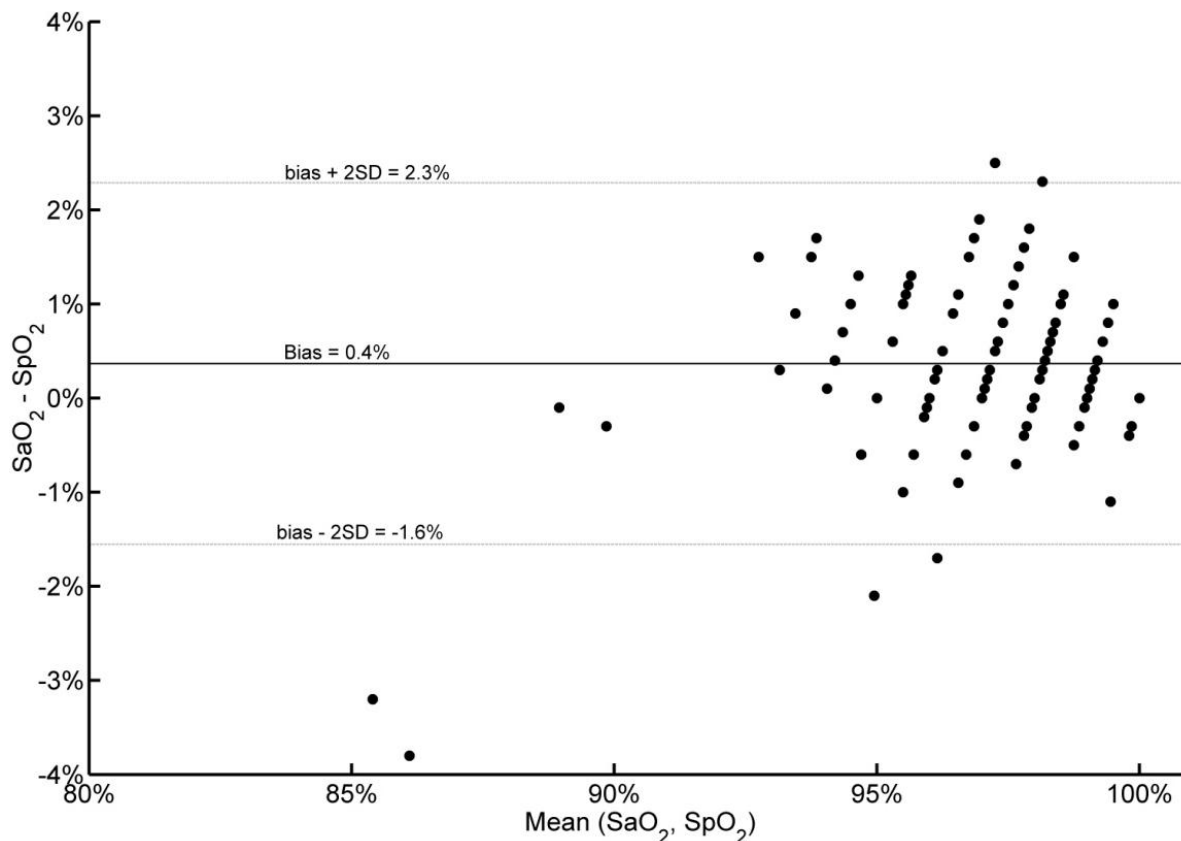


Figure 6 : Bland-Altman plot comparing measured arterial oxygen saturation and measured peripheral oxygen saturation. Bias and 95 % limits of agreement ( $\pm 2SD$ ) are shown.  $SD = 0.0098$ . (taken from Toftegaard et al. 2009 with permission from BMJ)

Figure 6 illustrates the accuracy and precision of the measurement of  $SpO_2$  in the patient population studied here, showing a mean bias of  $0.4 \pm 1.0\%$  (bias  $\pm SD$ ). These measurements enable calculations of arterial  $PO_2$  within  $\pm 1.85$  kPa ( $2SD$ ) for  $SpO_2$  levels less than or equal to 96 %, values which can be considered clinically useful. The precision of  $SpO_2$  measurement seen here is however better than that seen in other studies (13,14) where a  $SD$  closer to 2 % has been found. These previous studies had similar size patient groups to the present and similar patient heterogeneity, such that the explanation for the difference in precision is not clear.

Calculations of arterial  $pH$  and  $PCO_2$  could be performed with clinically acceptable accuracy, even with these larger errors in  $SpO_2$ , as shown in the previous sensitivity analysis (Rees et al. 2006). (Table 1)

## **Chapter four**

This chapter describes preliminary data collected from 15 very different children including healthy boys in the operating theatre (urology) and critically ill children in the paediatric intensive care unit.

Measured values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from venous, arterialised capillary and arterial blood are compared and furthermore the venous to arterial conversion method is applied to the data.

### **Patient material**

Arterial, venous and arterialised capillary blood samples were collected from 20 children belonging to one of two groups: Group I: children from the paediatric intensive care department; Group II: children from the urology department scheduled for urological procedures under general anaesthesia. Both departments were located at Aalborg University Hospital.

### **Data acquisition.**

For each child arterial, venous and arterialised capillary blood samples were taken simultaneously, i.e. within 10 seconds.

In Group II the blood samples were taken 3-5 minutes after anaesthesia induction, where hemodynamics and the respiratory function were deemed stable.

Arterial blood was sampled from an arterial catheter or by puncture of the arteria radialis, femoralis or brachialis as appropriate. Venous blood was sampled from vena femoralis, iliaca or subclavia ie. central venous blood. The arterialised capillary blood sample was taken from a prewarmed heel, fingertip or earlobe. In 7 of the children having venous or capillary blood sampled from more than one sampling site an additional arterial blood sample was taken immediately following sampling from all venous and capillary sites.

All blood samples were taken anaerobically (PICO and Clinitube, Radiometer) and analysed for acid-base and oxygenation (ABL Radiometer).

The quality of blood samples was assessed by comparing measured values of haemoglobin in the arterial blood with haemoglobin in the venous and capillary blood. Differences between arterial and venous or capillary haemoglobin values greater than 0.5 mmol/l were considered to indicate sampling and/or handling error and the blood samples were excluded from further analysis. This excluded one child from group I.

The blood samples from one child in group II was excluded as inspired oxygen fraction was high and unstable during the sampling process.

Ethical approval for the study was obtained from the Ethics Committee of North Jutland and Viborg Counties. Informed written and oral consent was obtained from the parent(s) or legal guardian in all cases.

## Statistical analysis

Measured values of arterial and venous or capillary blood pH, PCO<sub>2</sub>, and PO<sub>2</sub> were compared regardless of the venous or capillary sampling site. Differences between arterial and venous or capillary values are described using Bland-Altman plots and statistics calculated describing the mean difference (bias) and standard deviation (SD).

After application of the venous to arterial conversion method on the data the calculated arterial values of pH, PCO<sub>2</sub> and PO<sub>2</sub> were compared to the simultaneously measured arterial values using Bland Altman plots. Values of bias and standard deviation between measured and calculated arterial values are reported.  $\Delta BE_{av}$  has been set to zero and  $RQ = 0.82$  (Waldau et al. 2002).

## Results

The resulting study population with blood sampled from both venous and capillary sites consisted of 15 children, 7 from the paediatric intensive care department and 8 from the urology department. Their median age was 1.8 years, (range 2 month – 10.2 years), 13 males.

The demographics and diagnoses of the children are reported in table 8.

Patient number	Department	Diagnosis	Age	Sex
1	Paediatric Intensive Care	Respiratory insufficiency	2 month	Male
2	Paediatric Intensive Care	Acute lymphatic leukaemia and sepsis	1 years	Female
3	Urology	Inguinal hernia	1 years10 month	Male
4	Paediatric Intensive Care	Respiratory insufficiency	7 month	Male
5	Urology	Orkiopexi	3 tears 3 month	Male
6	Urology	Orkiopexi	3 years 7 month	Male
7	Paediatric Intensive Care	Pneumococcus meningitis	5 month	Female
9	Urology	Inguinal hernia	1 year 10 month	Male
10	Urology	Hydronephrosis	10 years 2 month	Male
12	Paediatric Intensive Care	Mesenterial cyst and sepsis	10 month	Male
13	Urology	Hydrocele	6 years 2 month	Male
14	Paediatric Intensive Care	Febrile seizure	9 month	Male
15	Urology	Urethral meatal stenosis	5 years 1 month	Male
16	Urology	Cryptorchidism	6 years 5 month	Male
17	Paediatric Intensive Care	Smoke poisoning	1 year 11 month	Male

Table 8: Demographics and diagnoses of the 15 children in the preliminary study.

Measured values of arterial, venous and capillary blood pH, PCO<sub>2</sub> and PO<sub>2</sub> for the two patient groups are shown in table 9.

		Pediatric Intensive Care			Urology		
		arterial	central venous	capillary	arterial	central venous	capillary
pH	minimum	7.333	7.297	7.299	7.270	7.248	7.297
	25 % quartile	7.349	7.327	7.353	7.327	7.311	7.350
	median	7.388	7.359	7.391	7.344	7.333	7.355
	75 % quartile	7.421	7.399	7.413	7.381	7.352	7.391
	maximum	7.464	7.436	7.469	7.414	7.416	7.425
PCO <sub>2</sub> kPa	minimum	3.94	4.34	4.47	4.52	4.47	4.26
	25 % quartile	5.17	5.77	5.16	4.83	5.55	4.49
	median	5.81	6.70	5.75	5.53	5.91	5.43
	75 % quartile	6.77	7.79	7.31	5.89	6.19	5.54
	maximum	8.70	9.46	8.71	6.61	7.21	5.96
PO <sub>2</sub> kPa	minimum	7.20	2.62	6.30	11.00	5.56	10.50
	25 % quartile	9.13	4.03	7.10	11.65	6.85	10.55
	median	10.70	4.90	7.81	13.90	7.64	11.00
	75 % quartile	11.93	5.26	9.22	15.45	9.09	12.90
	maximum	15.80	13.30	10.10	17.50	10.50	13.00

Table 9: Measured values of arterial, venous and capillary blood pH, PCO<sub>2</sub> and PO<sub>2</sub> for the two groups, Pediatric Intensive Care department and Urology department.

For the 7 children with two arterial blood samples, the differences between the two arterial samples were for pH  $-0.0006 \pm 0.012$  (mean $\pm$ SD), PCO<sub>2</sub> =  $-0.04 \pm 0.32$  kPa and PO<sub>2</sub> =  $0.47 \pm 1.35$  kPa. These values were not considered to be clinically different, illustrating that these patients had stable acid–base and oxygenation status during the study.

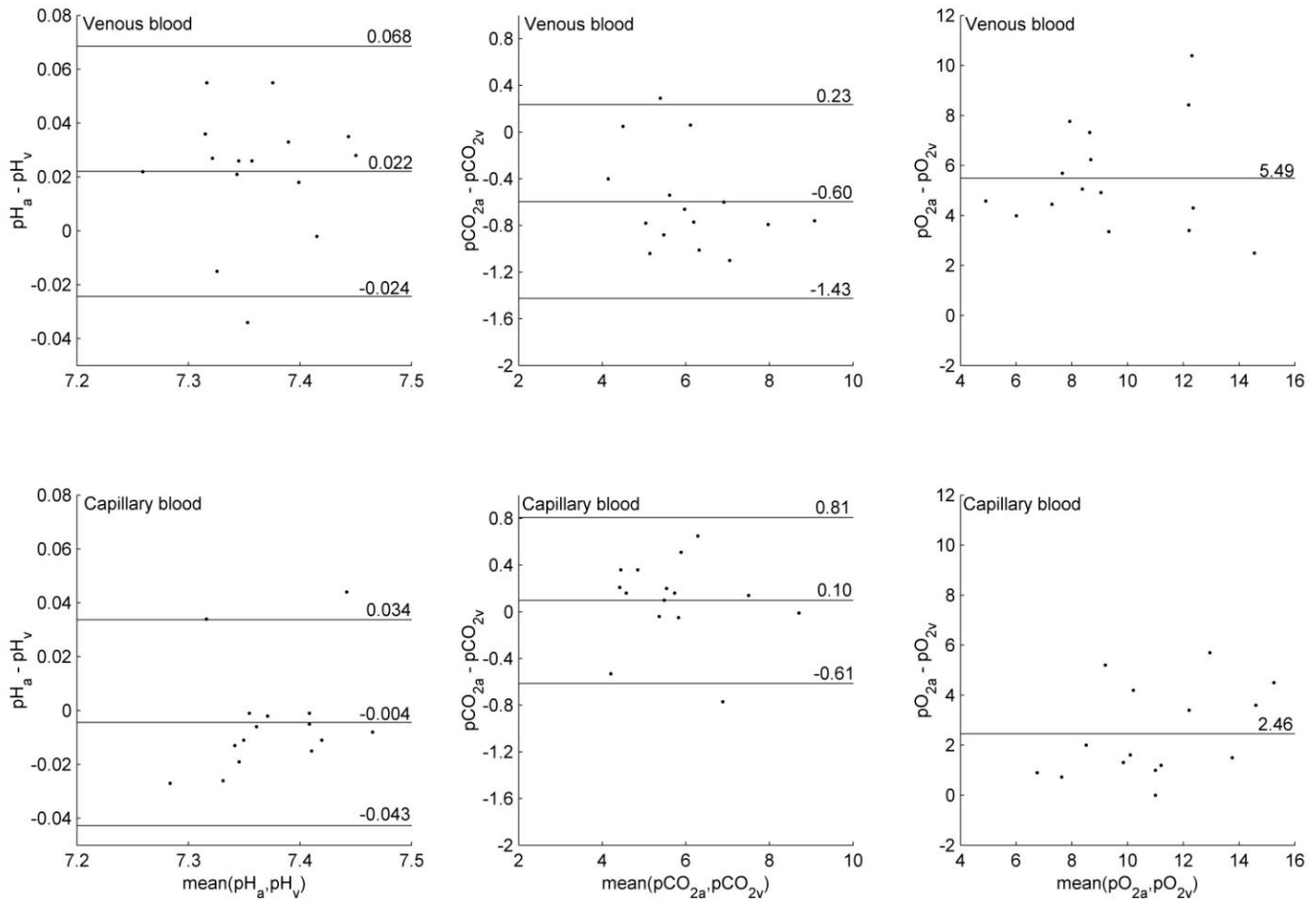


Figure 7 : Bland-Altman plots giving differences between measured arterial and venous values of pH, PCO<sub>2</sub> and PO<sub>2</sub> (upper row) or measured arterial and capillary blood (lower row). For pH and PCO<sub>2</sub> bias and 95 % limits of agreement ( $\pm 2SD$ ) are shown.

Figure 7 illustrates Bland–Altman plots comparing measured arterio-venous and arterio-capillary differences of pH, PCO<sub>2</sub> and PO<sub>2</sub>.

The arterio-capillary differences are small,  $-0.004 \pm 0.020$  (mean $\pm$ SD) for pH and  $0.10 \pm 0.36$  kPa for PCO<sub>2</sub>, indicating that the capillary blood is close to fully arterialised.

Despite the small number of children there seems to be a systematic increase in the difference between arterial and venous PO<sub>2</sub> with increasing PO<sub>2</sub> values, as was found in adults.

The SD describing the difference between arterial, capillary and venous values are given in table 10.

n=15	pH	PCO <sub>2</sub> (kPa)
± 2 SD of Arterial – Venous	0.022 ± 0.046	-0.60 ± 0.83
± 2 SD of Arterial – Capillary	-0.004 ± 0.038	0.10 ± 0.71
Laboratory acceptable performance criteria (acceptable range)	± 0.04	± 0.67 <sup>a</sup>

Table 10: Bias ± 2 SD for the difference between arterial, venous and capillary blood, compared to laboratory performance guidelines. It is assumed that these guidelines are comparable to a 95% confidence interval given by 2 SD. <sup>a</sup>Original value given as ± 5 mmHg.

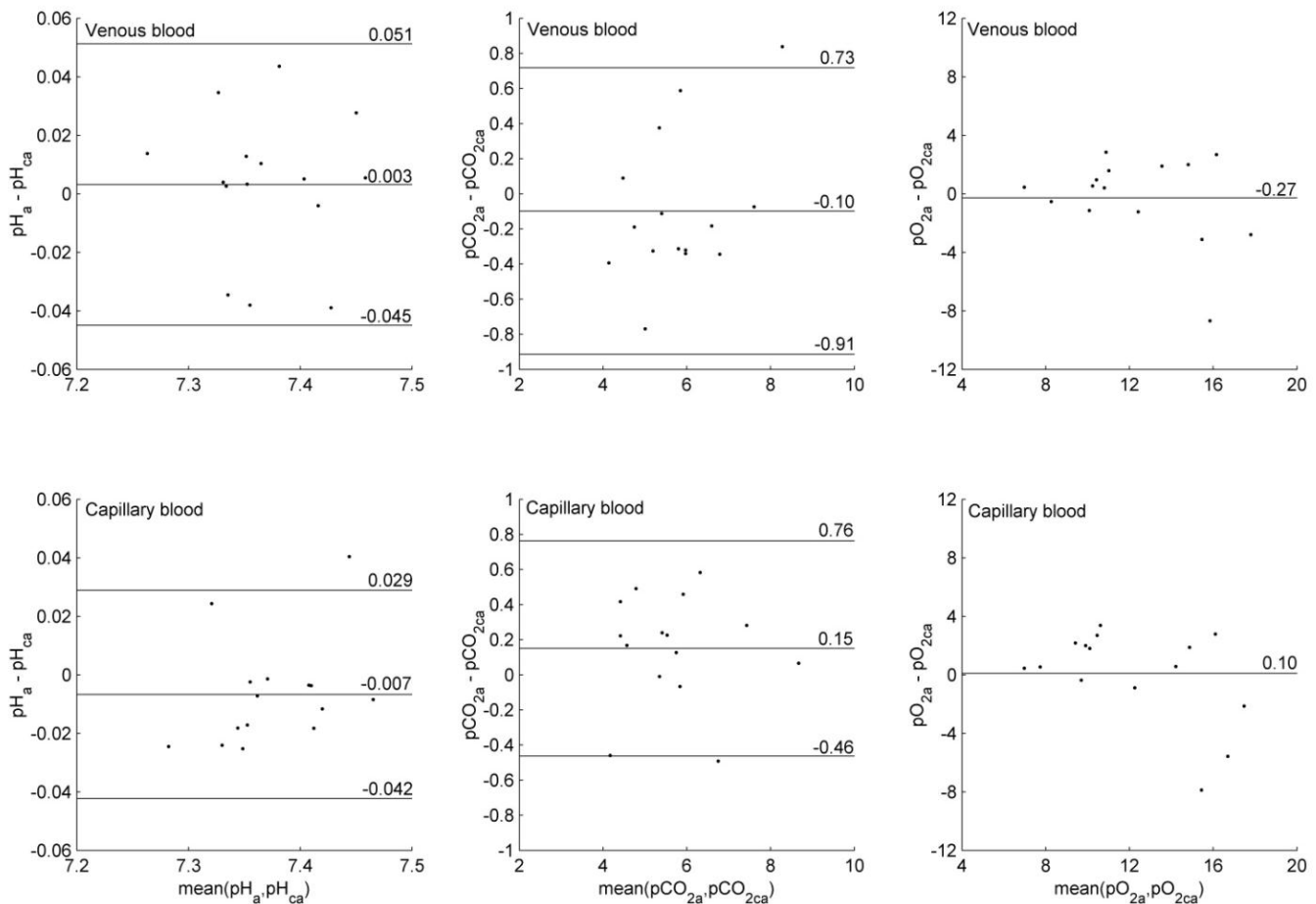


Figure 8 : Bland-Altman plots comparing measured arterial (a) and calculated arterial (ca) values of pH, PCO<sub>2</sub> and PO<sub>2</sub> from venous and capillary blood. Bias and 95 % limits of agreement (± 2SD) are shown for pH and PCO<sub>2</sub>. For pH (venous and capillary blood) SD was 0.025 and 0.018 respectively. For PCO<sub>2</sub> (venous and capillary blood) SD was 0.42 kPa and 0.31 kPa respectively.

Figure 8 and table 11 illustrate the difference between measured arterial values (a) and calculated arterial values (ca) using the venous to arterial conversion method on venous blood (upper row) and capillary blood (lower row).

	pH	PCO <sub>2</sub> (kPa)	PO <sub>2</sub> (kPa)
Arterial – calculated arterial values from venous blood (n=15)	0.003 ± 0.048	-0.10 ± 0.82	-0.27 ± 5.78
Arterial – calculated arterial values from capillary blood (n=15)	-0.007 ± 0.036	0.15 ± 0.61	0.10 ± 6.23
Laboratory acceptable performance criteria (acceptable range)	± 0.04	± 0.67 <sup>a</sup>	± 0.6 <sup>b</sup>
Arterial – arterial variability (n=7)	± 0.024	± 0.637	± 2.705

Table 11 : Bias ± 2SD for the difference between arterial and calculated arterial blood values from venous and capillary blood, compared to laboratory performance guidelines.

It is assumed that these guidelines are comparable to a 95% confidence interval given by 2 SD. <sup>a</sup>Original value given as ± 5 mmHg. <sup>b</sup>Original value given as ± 3 SD of measurement equipment error, where one SD is assumed to be 0.2 kPa according to Radiometer Medical A/S 1994.

The calculated values of arterial pH and PCO<sub>2</sub> have small bias and standard deviations, the SD being marginally larger than in the adult population study. In capillary blood these errors are within those considered acceptable for the performance of laboratory equipment (table 11) (Burtis & Ashwood 1999; Department of Health and Human Services 1998) and within the limits of error acceptable in clinical practice. In venous blood the bias has been substantially reduced, relative to the bias of the arterio-venous difference. The SD are just above the value considered acceptable for the performance of laboratory equipment, but might still be within the limits of error acceptable in clinical practice.

For PO<sub>2</sub> the errors are clearly outside the limits of error acceptable in clinical practice, but due to the small number of patients no conclusion can be made.



### **Conclusion of the pediatric study**

This small preliminary study of 8 healthy and 7 very ill children from the two groups show almost the same results with regards to pH and PCO<sub>2</sub> as in the adult study, even though the venous blood was sampled from different sites, depending on accessibility.

As in the adult study the results from the application of the method on the venous and capillary blood values show a reduction of arterio-venous bias. The SDs were marginally larger than in the adult study.

The results with PO<sub>2</sub> show a larger SD than in the adult study.

The measurement of SpO<sub>2</sub> in the pediatric population show a mean bias of  $1.1 \pm 1.3$  % (bias  $\pm$  SD). The precision of SpO<sub>2</sub> measurement seen here are less than that seen in the adult study ( $0.4 \pm 1.0$  % (bias  $\pm$  SD)), which could explain the larger SD of PO<sub>2</sub>.

Nevertheless the results indicate a possible use of the method in the pediatric population, as the application of the method on sampled blood either from venous or capillary sites is safe and could spare the child from an arterial puncture.

## Conclusion of the thesis

In chapter 1 the new method of converting venous values of acid-base and oxygenation status to arterial values has been described in detail.

The method simulates a reversal of the transport of blood from the veins to the arteries.

Two assumptions are made. First it is assumed, that the amount of strong acid added to the blood on its passage through the tissues is very small or zero. Second a constant value of RQ is used. The endpoint in the calculations used is the measured peripheral oxygen saturation. The model then calculates the “arterialised” values of acid-base and oxygenation.

The method is tested for the sensitivity of measurement errors, handling errors and assumptions, and the tests show that the method is quite insensitive to these points except in the calculation of  $PO_2$  from  $SpO_2$  above 97 % due to the flat shape of the oxygen dissociation curve (ODC).

In chapter 2 the measured data from the adult study with blood from anaerobically sampled peripheral, central and mixed veins are presented as a direct comparison between venous and arterial values. The results show a reasonable correlation between the venous and arterial pH and  $PCO_2$  from all three sampling sites, but with a physiologic difference (bias) that represents a necessary correction for converting the venous values to arterial values. There was no correlation between venous and arterial  $PO_2$ .

These results indicate that venous blood sampled anaerobically could be used to estimate arterial pH and  $PCO_2$  but certainly not  $PO_2$ .

In chapter 3 we then tested the new venous to arterial conversion method on the measured data from the adult study.

The results show that the calculated arterial values of pH and  $PCO_2$  have a precision within laboratory acceptable performance criteria and similar to the variability between consecutive arterial blood samples. These results were seen from all three venous sampling sites, but with the greatest precision when calculated from peripheral venous blood, making this method very applicable for many different patient types outside the intensive care departments.

The method provides a significant improvement to direct correlation between arterial and venous values. For peripheral venous blood the SD of calculated arterial pH and  $PCO_2$  are half that seen for direct correlation between measured arterial and venous blood, meaning that the method offers a great improvement on the information obtained from peripheral venous blood.

For SpO<sub>2</sub> values less than or equal to 96 % the method calculated PO<sub>2</sub> with a similar variability as between consecutive arterial blood samples. For SpO<sub>2</sub> greater than 96 % the method is not able to calculate PO<sub>2</sub> within an acceptable clinical range.

In clinical use the most important patients are those with low values of SpO<sub>2</sub> which potentially makes the method very useful for screening and monitoring these patients.

In chapter 4 the method is tested on 15 children of very different ages and health.

Both central venous and capillary blood was tested.

The results with regards to pH and PCO<sub>2</sub> are very similar to the results from the adult study, except that the standard deviations are marginally larger.

The results with PO<sub>2</sub> show a larger SD than in the adult study, partly explained by a lesser precision of SpO<sub>2</sub> measurement in the pediatric population.

Nevertheless the method is useful in the pediatric patient population, as it corrects for the arteriovenous gradient (bias) and does the child no further harm, as no extra blood sampling are necessary. As for the adults the method can therefore be used as a screening tool.

The conclusion of the thesis is therefore that the venous to arterial conversion method has a great potential for use as a screening tool in both emergency medical or pediatric departments. In pediatric, medical and surgical wards the method could be used to assess a patient's acid-base and oxygenation status prior to the decision to sample arterial blood or to help in the decision to refer the patient to the intensive care unit. In departments where arterial blood gas values are used to monitor patients, i.e. pulmonary medicine, the method might be used to reduce the number of arterial samples taken, these being replaced by peripheral venous or capillary blood samples, reducing the need for painful arterial punctures.

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## Dansk resume

Analyse af arterieblod med beskrivelse af syre-base status, oxygenering og elektrolyt indhold er et vigtigt redskab for at vurdere den metaboliske, kardiovaskulære og respiratoriske tilstand hos en patient. På intensive afdelinger og andre semi-intensive observationsafsnit tages arterielle blodprøver hyppigt og ofte mange gange dagligt. I skadestuer, modtagelser og andre specialiserede afdelinger såsom lungemedicinske og nyremedicinske afdelinger er arterieblodprøver også en vigtig del af den daglige monitorering og sker ved punktur af en perifer arterie.

På medicinske og kirurgiske sengeafdelinger er arterieblodprøver ikke rutine og tages typisk, hvis en patients kardiovaskulære og/eller respiratoriske tilstand forværres, eller hvis lægen behøver mere information.

Derimod tages perifert venøse blodprøver som et af de første diagnostiske tiltag ved indlæggelse på sygehus, og også hyppigt på indlagte patienter.

Veneblod og specielt perifert veneblod bruges normalt ikke til at beskrive en patients metaboliske og respiratoriske tilstand, undtagen i enkelte specielle situationer, hvor centralt veneblod kan give oplysninger.

Flere studier har undersøgt brugen af veneblod til at vurdere syre-base status, de fleste har dog kun undersøgt sammenhængen mellem arterie og veneblod i forhold til en enkelt variabel (pH eller  $PCO_2$ ). Disse studier har generelt fundet en god sammenhæng for pH og en mindre god for  $PCO_2$  i undersøgelser af patienter, der ikke undersøges i hjertestop situationer. Der er ikke fundet sammenhæng mellem arteriel og venøs  $PO_2$ .

Der er udviklet metoder til at "arterialisere" venøst blod ved at opvarme prøvetagningsstedet, hvilket øger blodstrømningshastigheden, således at venøst blod får samme karakteristika som arterielt blod. Disse metoder kræver ekstra udstyr og tager tid, hvilket gør dem mindre klinisk brugbare.

Denne afhandling beskriver og evaluerer en metode til at omregne venøse blodprøveværdier til arterielle værdier. Metoden inkluderer måling af den perifere iltmætning. Både syre-base og oxygeneringsværdier rapporteres.

Afhandlingen inkluderer data fra 2 studier, det ene med 103 voksne patienter og det andet med 15 børn i alle aldre.

Kapitel 1 beskriver den nye metode i detaljer inklusive de fysiologiske forudsætninger, analyse af nøjagtighed og mulige begrænsninger for metoden.

Princippet i metoden er at beregne arterielle værdier ved, med brug af matematiske modeller, at simulere den omvendte transport af blod fra vene til arterie indtil den simulerede iltmætning i arterieblodet er lig den målte perifere iltmætning.

Anvendelsen af metoden illustreres med data fra 3 patienter med forskellige syre-base, hæmodynamiske og metaboliske tilstande. Metodens følsomhed testes for målefejl, fejl p.g.a. de fysiologiske forudsætninger og fejl p.g.a. luftbobler i blodprøven.

Følsomhedstesten viser at metoden er meget ufølsom for disse forhold undtagen i beregningen af  $PO_2$  ved iltmætning større end 97 % på grund af den flade hældning på ilt dissociations kurven.

I kapitel 2 beskrives data fra voksenstudiet. De målte værdier for pH,  $PCO_2$  og  $PO_2$  fra arterie- og veneblod sammenlignes. Veneblod er taget fra både perifere og centrale vener samt fra lungearterien.

Resultaterne viser at de venøse værdier af pH, korrigeret for middelforskellen (bias), kan give arterielle værdier tæt på laboratorie standarder. Dette gælder også for  $PCO_2$ , undtagen fra perifert veneblod.

For  $PO_2$  er den arteriovenøse bias ikke normalfordelt, og størrelsen af bias og standardafvigelsen (SD) viser tydeligt, at veneblod ikke kan bruges til at estimere arterielle værdier.

I kapitel 3 anvendes data fra voksenstudiet til at udregne arterie værdier ud fra venøse værdier ved brug af vene til arterie udregningsmodellen.

I resultaterne ses, at de beregnede arterielle værdier for pH og  $PCO_2$  ligger meget tæt på de målte arterielle værdier, uanset hvor veneblodet tages fra. Beregninger udført på værdier fra perifert veneblod er dog signifikant mere præcise end hvis blodet tages fra en central vene.

Endvidere er SD på de beregnede værdier for pH og  $PCO_2$  lig med SD ved to på hinanden følgende arterieblodprøver.

For perifert veneblod ses, at SD på beregnede arterielle værdier for pH og  $PCO_2$  kun er halvt så stor som SD ved direkte sammenligning af arterielt og venøst blod. Dette betyder, at beregninger udført med den nye metode øger kvaliteten af informationer fra veneblodprøver.

Ved perifer iltmætning  $< 97\%$  kan metoden beregne  $PO_2$  med den samme variation som ses ved to på hinanden følgende arterieblodprøver. Ved perifer iltmætning  $\geq 97\%$  kan metoden ikke beregne  $PO_2$  med tilstrækkelig nøjagtighed. I kliniske sammenhænge er patienter med lav perifer iltmætning mest hastende, hvorfor den nye metode kan blive et vigtigt redskab til screening og monitorering af sådanne patienter.

I kapitel 4 beskrives resultaterne fra børnestudiet. I første del sammenlignes de målte værdier for pH,  $PCO_2$  og  $PO_2$  fra vene- og kapillærblod med målte værdier fra arterieblod. Derefter beregnes arterielle værdier ved brug af vene til arterie udregningsmodellen ud fra målte værdier fra vene- og kapillærblod.

Resultaterne ved beregning af arteriel pH og  $PCO_2$  med vene til arterie udregningsmodellen svarer til resultaterne fra voksenstudiet med en tilsvarende reduktion af bias og en SD, der er marginalt større.

Ved beregning af arteriel  $PO_2$  ses en større SD end i voksenstudiet, delvis forklaret ved en større unøjagtighed ved måling af perifer iltmætning på børnene.

Resultaterne fra børnestudiet giver potentiale for brug af vene til arterie udregningsmodellen, da anvendelsen af metoden på vene- eller kapillærblod er ufarlig og kan skåne barnet for en arteriepunktur.

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